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Sodium Borohydride on Wet Clay: Solvent-free Reductive Amination of Carbonyl Compounds Using Microwaves†

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Abstract: A solvent-free reductive amination of carbonyl compounds by wet montmorillonite K 10 clay supported sodium borohydride is described; microwave irradiation facilitates the procedure.

The reductive amination of carbonyl compounds is one of the most useful reactions for the synthesis of amines and their derivatives[1] as these compounds are known to have herbicidal and fungicidal activities,[2] and constitute important precursors to a variety of agents that are of interest to pharmaceutical and agricultural industries.[3] The Borch reduction using sodium cyanoborohydride [$NaBH_3CN$][4] and reductive amination using sodium triacetoxyborohydride [$NaBH(OAc)_3$][5] are the two very popular methods to achieve this transformation. However, the first method has the risk of residual cyanide in the products or in the workup waste stream whereas the later involves the use of corrosive acetic acid. Recently, the N-alkylation of primary aromatic amines has also been reported using $NaBH_4$ that is conducted in sulfuric acid medium.[6] Consequently, there is a need for the development of a manipulatively easy and an environmentally friendly method for the reduction of *in situ* generated Schiff's bases.

Heterogeneous reactions facilitated by supported reagents on various solid inorganic surfaces have received attention in recent years because of the greater selectivity and simple reaction work-up.[7] Microwave (MW) heating has been used for the rapid synthesis of a variety of organic compounds[8-11] both in solution phase[9] as well as under solvent-free conditions.[10,11] The salient features of the microwave approach coupled with the use of mineral supported reagents or catalysts are the enhanced reaction rates, formation of pure products in high yields and the ease of manipulation. Further, the solventless microwave-assisted reactions[10,11] are now gaining popularity as they provide an opportunity to work with open vessels, thus avoiding the risk of high pressure development and with a possibility of upscaling the reactions on preparative scale.

During the course of our ongoing program to develop environmentally benign solvent-free methods,[11] we have discovered methods for the rapid synthesis of imines and enamines via reactions that are catalyzed by clay[11i] and Envirocat reagent, EPZG®,[11j] wherein elimination of water is facilitated by exposure to microwaves. Herein, we report a facile method for the synthesis of secondary and tertiary amines using a solvent-free system, $NaBH_4$–wet clay coupled with microwave activation.

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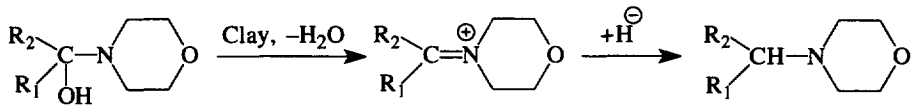
RESULTS AND DISCUSSION

We investigated the reducing ability of $NaBH_4$–wet clay for the reduction of *in situ* generated Schiff's bases. The solid state reductive amination of carbonyl compounds is explored on various inorganic solid supports such as alumina, clay, silica etc. and found that among these materials clay afforded the best results. Clay not only behaves as an acid but also provides water from its interlayers that is responsible for the acceleration of the reducing ability of $NaBH_4$.[12] The important role of clay is apparent from the fact that only poor yield (~10%) was obtained without this support as exemplified for the product, N-phenyl-*p*-chlorobenzylamine (Table, entry 6), Although these reactions are very facile yet the efficiency may be further enhanced by conducting the reactions in partially sealed containers.

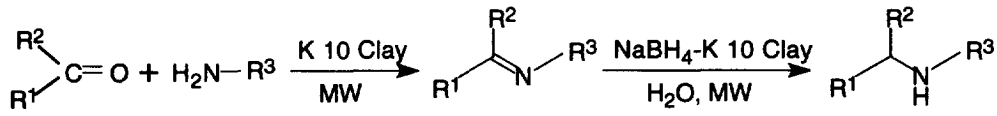
The process in its entirety involves a simple mixing of *in situ* generated imines,[11i] with 10% $NaBH_4$-wet clay and irradiating the reaction mixture in an unmodified household microwave oven for the time specified in the Table. The reagent is more effective when the Schiff's base is first mixed with $NaBH_4$ and clay and then wetted with water. A simple extraction of the product from the solid support affords the corresponding amines in high yields. In some cases, the reduction of imines is completed immediately upon mixing with clay supported $NaBH_4$ at room temperature. However, the reactions involving Schiff's bases generated from cyclohexanone and aniline (entry 12) and aliphatic aldehydes and amines (entry 14) require a relatively longer time for completion. The reduction of the substrates bearing electron withdrawing substituents (entries 5, 10) is relatively slow in comparison to those with electron donating groups (entries 8, 9). No side product formation is observed in any of the reactions investigated. Interestingly, the dehalogenation of the compounds (entries 6, 7 and 11) is not observed under these conditions.[13,14] For low boiling reactants, the reaction mixtures are irradiated with intermittent heating [pulsed sequence with an interval of 1 min between two successive irradiations of 2 min each at low MW power (20%)]. This pulse protocol is required to maintain the bath temperature at ~65 °C to avoid the loss of low boiling n-propylamine (entry 20, see details in experimental section).

In the reactions of ketones with secondary amines (entries 23, 24), where enamine formation is expected, the intermediate carbinol amines dehydrates to generate iminium ions in the presence of acidic K 10 clay which, in turn, accept hydride ions from $NaBH_4$ to afford tertiary amines (Eqn. 1). This acidity dependent generation of hydride species from $NaBH_4$ on clay surface, which is responsible for the reduction of the Schiff' bases, has not been fully exploited.[5,6]



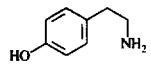
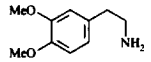
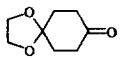
(Eqn. 1)

That the effect may not be purely *thermal*[15] is evident from the fact that for similar product yields a much longer time period is required for completion of the reaction (5h, entry 6) at the same temperature of 65 °C using an alternate heating mode (oil bath).



Scheme

Table. Reductive Amination of Carbonyl Compounds using $NaBH_4$ Supported on K 10 Clay

Entry	Carbonyl Compounds	Amines	Time[a] (min)	Yield[b] (%)	m.p.(°C) or b.p. (°C)/torr	
					Observed	Reported
1	Benzaldehyde	Aniline	<5.00	97	37-38	35.5-37.8[17]
2	Benzaldehyde	n-Heptylamine	<5.00	94	167-169[c]	166-170[18]
3	Benzaldehyde		1.50	90	141-142	143[19]
4	Salicylaldehyde	Aniline	<5.00	96	111-112	113[20]
5	Salicylaldehyde	*p*-Nitroaniline	1.00	88	136-137	138[21]
6	*p*-Chlorobenzaldehyde	Aniline	0.50	90	209-211[c]	210-211[16]
7	*p*-Chlorobenzaldehyde	*o*-Aminophenol	0.75	84	108-109	109[21]
8	*p*-Anisaldehyde	Aniline	0.25	93	46-48	48-49[16]
9	*p*-Anisaldehyde	*p*-Aminophenol	0.75	81	101-103	102-103[23]
10	*p*-Nitrobenzaldehyde	Aniline	1.25	78	67-69	67-68[22]
11	3,4-Dimethoxybenzaldehyde	*p*-Chloroaniline	0.50	91	122-123	123[21]
12	Isobutyraldehyde	Aniline	1.00	78	204-206[c]	206[24]
13	2-Ethylbutyraldehyde	Aniline	0.75	87	113-115[e]	114-115[25]
14	2-Ethylbutyraldehyde	n-Decylamine	1.50	86	66-69/8	f
15			1.50	81	145-147	147[21]
16	Acetophenone	Aniline	1.50	92	121-124/3	122-124/3[28]
17	Acetophenone	Benzylamine	2.00	66	178-180[c]	179-181[5]
18	Cyclohexanone	Aniline	1.00	89	105-108/3	112-113/3[26]
19	4-Methylcyclohexanone	Benzylamine	2.00	85	98-99[e]	97-98[27]
20	Cycloheptanone	Propylamine	0.75	79	205-207[c]	207-208[5]
21		Benzylamine	1.50	91	241-243[d]	245-246[5]
22	3-Pentanone	Aniline	1.00	83	83-86/8	56-67/3-4[26]
23	2-Heptanone	Morpholine	2.00	81	150-151[c]	151-153[5]
24	2-Heptanone	Piperidine	2.00	78	159-161[c]	160-161[5]

[a]Time for the reduction of *in situ* generated Schiff's bases in microwave oven. The time, <5.00 min, refers to the reductions at room temperature that are completed on simple mixing of the Schiff's base with $NaBH_4$-wet clay. [b]Unoptimized yields of purified bases that exhibited physical and spectral properties in accord with the assigned structures. [c]Hydrochloride salt. [d]Oxalate salt. [e]*p*-Toluenesulfonyl derivative. [f]See experimental section.

In conclusion, we have developed a facile and practical method for the reductive amination of carbonyl compounds under solvent-free conditions using $NaBH_4$-wet clay, that is accelerated by microwave irradiation.

EXPERIMENTAL SECTION

General. All reagents were purchased from Aldrich Chemical Co. or Lancaster Synthesis Inc. and were used as received. Some aldehydes were distilled prior to use. A Sears Kenmore microwave oven (900 Watts) equipped with a turntable was used for microwave heating. An alumina bath (neutral alumina: 125 g, mesh ~150, Aldrich; bath: 5.7 cm diameter) was used as a heat sink inside the MW oven to irradiate the reaction mixtures in all experiments. TLC was performed on silica gel plates obtained from Analtech, Inc. using Hexane:EtOAc (9:1, v/v) as the solvent system. Melting points were determined on a Mel-Temp II hot stage

apparatus using Fluke 51 K/J digital thermometer and are uncorrected. IR spectra were recorded on a Perkin-Elmer 1310 spectrophotometer. NMR spectra were recorded in $CDCl_3$ on a Jeol Eclipse (300 MHz for ^1H NMR and 75 MHz for ^{13}C NMR) spectrometers using TMS as an internal standard. Mass spectra were recorded on a Hewlett Packard® 5890 mass spectrometer (70 eV) using a GC/MS coupling or direct inlet system. The identity of the compounds were confirmed by comparison of their physical and spectral data with those reported in the literature including their derivatization into various salt forms. The reagent, 10% $NaBH_4$-clay, is prepared by mixing $NaBH_4$ (0.5 g) with montmorillonite K 10 clay (4.5 g) in solid state using a pestle and mortar.

CAUTION. Although we did not encounter any accident during these studies, we recommend extreme caution for reactions conducted on larger scales because of the possible higher localized temperatures attained in the microwave oven.

Typical Procedure. The synthesis of N-phenyl-*p*-chlorobenzylamine is representative of the general procedure employed. A mixture of *p*-chlorobenzaldehyde (0.7 g, 5 mmol), aniline (0.455 g, 5 mmol) and montmorillonite K10 clay (0.1 g) contained in a 25 mL beaker was placed in an alumina bath inside the microwave oven and irradiated for 2 min. The *in situ* generated Schiff's base was mixed thoroughly with freshly prepared $NaBH_4$-clay (5.0 mmol of $NaBH_4$ on 1.72 g of reagent) and water (1 mL). The reaction mixture was again irradiated for 30 sec (65 °C). Upon completion of the reaction, monitored on TLC, the product was extracted into methylene chloride (3x15 mL). The removal of solvent under reduced pressure provided pure N-phenyl-*p*-chlorobenzylamine in 90% yield. The identity of the product was confirmed by formation of the hydrochloride salt, m.p. 209-211 °C (EtOAc-MeOH) (lit. m.p. 210-211 °C).[16]

N-(2-Ethylbutyl)-1-decylamine (entry 14). The same procedure described for the preparation of N-phenyl-*p*-chlorobenzylamine provided a free base in 86 % yield, b.p. 66-69 °C/8 torr. A small portion of the free base was converted into its HCl salt, white solid, m.p. 148-151°C (EtOAc-MeOH), ^1H NMR (free base, $CDCl_3$): δ 0.79-0.87 (m, 9H), 1.19-1.30 (m, 20H), 1.39-1.44 (m, 1H), 1.46 (bs, 1H), 2.45 (d, J = 7.3 Hz, 2H), 2.5 (t, J = 7.2 Hz). ^{13}H NMR (free base, $CDCl_3$): δ 10.9 (CH_3), 14.2 (CH_3), 22.7 (CH_2), 24.1 (CH_2), 27.5 (CH_2), 29.4 (CH_2), 29.7 (CH_2), 30.2 (CH_2), 31.9 (CH_2), 40.8 (CH), 50.4 (CH_2), 52.9 (CH_2). IR (Nujol): 3423 (w, N–H stretching) 1565 (m, N–H bending) cm^{-1}. EI MS m/z (relative intensity) 241 (M^+, 9), 170 (M^+-71, 100), 114 (18), 84 (12), 70 (16), 55 (32), 45 (M^+-196, 100), 44 (96).

N-(1-Propyl)aminocycloheptane (entry 20): A mixture of cycloheptanone (0.56 g, 5 mmol), n-propylamine (0.46 g, 7.5 mmol) and K 10 clay (0.1 g) contained in a small beaker was placed in an alumina bath (heat sink) and irradiated for 6 min in a MW oven at its 20% power using pulsed method (one min cooling between two successive irradiations of 2 min each). The *in situ* generated Schiff's base was mixed with sodium borohydride (0.19 g, 5 mmol) and K 10 clay (1.53 g) to which water (1 mL) was added and the reaction mixture was irradiated in MW oven for 45 sec at its full power. Upon completion of the reaction, as monitored on TLC, the product was extracted into methylene chloride (3x15 mL). The removal of the solvent under reduced pressure gave the free base in 79 % yield. HCl salt (EtOAc-MeOH), m.p. 205-207 °C (lit. m.p. 207-208 °C).[5]

All the results reported in the Table refer to the reactions that are conducted on a 5 mmol scale. The reaction of *p*-anisaldehyde with aniline (entry 8), at a relatively larger scale (50 mmol), undergoes completion in 30 sec to afford N-phenyl-*p*-methoxybenzylamine in 91% yield.

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