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SOLVENT-FREE SOLID SUPPORTED AND PHASE TRANSFERRED CATALYZED SYNTHESIS OF BENZANILINE DERIVATIVES USING MICROWAVE IRRADIATION

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ABSTRACT

In this study, solvent-free and phase transfer catalysis conditions coupled with microwave irradiation and their advantages in synthesis of N-alkylation of primary anilines were reported. In this way two different microwave processing techniques were compared in terms of reaction yields. Consequently, microwave irradiation significantly reduced reaction times compared to traditional heating methods. Particularly synthesis by solvent-free solid supported microwave irradiaton was found more eco-friendly and had higher reaction efficiency against to phase transfer catalysis condition. Organic reactions under solvent-free conditions is advantageous because of enhanced selectivity, efficiency and more importantly, toxic and volatile solvents are avoided. So that this eco-friendly green approach might be applied to the rapid assembly of various alkylation reactions.

INTRODUCTION: Since the initial experiments in the mid-1980s, the use of microwave energy for heating chemical reactions has shown tremendous benefits in organic synthesis. Significant rate enhancements, improved yields, and cleaner reaction profiles have been reported for many different reaction types over the past two decades. Thus, when planning a reaction protocol or designing novel synthetic pathways, the use of microwave irradiation as heating source should become a first choice and not the last resort [1].

A frequently used processing technique employed in microwave-assisted organic synthesis since the early 1990s involves solvent-less ("dry media") procedures [2-7] where the reagents are pre-adsorbed onto either an essentially microwave-transparent (silica, alumina or clay) or a strongly absorbing (graphite) inorganic support, that additionally can be doped with a catalyst or reagent. An alternative technique utilizes microwave-transparent or only weakly absorbing inorganic supports such as silica, alumina or clay [2-7].

These reactions are effected by the reagents/substrates immobilized on the porous solid supports and have advantages over the conventional solution-phase reactions because of their good dispersion of active reagent sites, associated selectivity, and easier work-up. The recyclability of some of these solid supports and the avoidance of the waste disposal problems associated with the use of solvents, render these processes ecofriendly "green" protocols. In general, the substrates are pre-adsorbed onto the surface of the solid support and then exposed to microwave irradiation.

In addition to solvent-free processing, phase-transfer catalytic conditions (PTC) have also been widely employed as a processing technique in MAOS (Microwave Assisted Organic Synthesis) [3, 8]. In phase-transfer catalysis, the reactants are situated into two separate phases, for example liquid-liquid or solid-liquid. In liquid-liquid PTC, because the phases are mutually insoluble, ionic reagents are typically dissolved in the aqueous phase, while the substrate

remains in the organic phase. On the other hand, in solid-liquid PTC, ionic reagents may be used in their solid state as a suspension in the organic medium. Transport of the anions from the aqueous or solid phase to the organic phase is facilitated by phase-transfer catalysts, typically quaternary onium salts or cation-complexing agents. Phase-transfer catalytic reactions are perfectly tailored for microwave activation, and the combination of solid-liquid PTC and microwave irradiation typically gives the best results in this area [3, 8].

Numerous transformations in organic synthesis can be achieved under solid-liquid PTC and microwave irradiation in the absence of solvent, generally at atmospheric pressure in open vessels.

In this study various primary anilines were N-alkylated with benzyl chloride and 4-methylbenzyl chloride under solvent-free solid supported and phase-transfer-catalysis conditions with microwave irradiation. In this way two different microwave synthesis methods were compared in terms of reaction yields.

MATERIALS AND METHODS:

Materials: The ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectras were recorded with tetramethylsilane (TMS) as the internal standard on a Bruker FT-400 MHz spectrometer by using $CDCl_3$ as the solvent. Melting points of all compounds were obtained on Electrothermal 9100 melting-point apparatus. Benzaniline compounds were synthesized with CEM (Discover Model) microwave laboratory oven. Reaction progress and product mixtures were routinely checked by thin-layer chromatography (TLC) on Merck SilicaGel F254 aluminum plates.

Column chromatography was performed with silicagel (70–230 Mesh). p-Anisidine, p-toluidine, 4-chloroaniline, p-phenetidine, 4-ethylaniline, 4-nitroaniline, 4-fluoroaniline, benzylchloride, 4-methylbenzylchloride, tetra-butylammonium bromide (TBAB), K_2CO_3 and supported reagent Al_2O_3 (pH=10±0.5) were purchased from Sigma-Aldrich. 4-Bromoaniline, 4-iodoaniline were obtained from Merck Chemicals.

Methods:

General synthesis procedure under Phase-Transfer-Catalysis conditions: A mixture of substituted aniline (10 mmol), benzyl chloride or p-methylbenzyl chloride (5 mmol), potassium carbonate (6.25 mmol) and TBAB (1 mmol) in 3-5 ml toluene was added into a 10 ml glass tube with a magnetic stirring bar and sealed with a plastic cap. The synthesis was carried out under microwave irradiation. Completion of the reaction was checked by TLC and all of the compounds were purified by column chromotography on silica gel. All physical constants of compounds were given in **Table 1**. Synthesis pathway is shown on **Scheme 1**.

TABLE 1: CHARACTERIZATION DATA OF BENZANILINE DERIVATIVES

			Yield (%)					M.W.	
Compound	R1	R2	ptc	solid	m.p (oC)	Chemical Formula	Mol. Weight	Watt	Time (min)
1	NO2	CH3	5	11	183-185	$C_{14}H_{14}N_2O_2$	242,11	100	5
2 9	NO2	H	7	17	146	$C_{13}H_{12}N_2O_2$	228,09	90	4
3 10	C2H5	CH3	40	65	a	$C_{16}H_{19}N$	225,15	120	10
4 11	C2H5	H	54	70	a	$C_{15}H_{17}N$	211,14	360	4
5 12	OCH3	CH3	64	53	b	$C_{15}H_{17}NO$	227,13	360	2
6 13	OCH3	H	66	72	52	$C_{14}H_{15}NO$	213,12	360	2
7	OC2H5	CH3	52	78	63-65	$C_{16}H_{19}NO$	241,15	360	2
8 14	OC2H5	H	55	85	45	$C_{15}H_{17}NO$	227,13	360	2
9 15	CH3	CH3	40	69	52	$C_{15}H_{17}N$	211,14	360	4
10 16	CH3	H	46	37	20	$C_{14}H_{15}N$	197,12	360	4
11 12	Cl	CH3	65	79	53	$C_{14}H_{14}ClN$	231,08	360	2
12 13	Cl	H	54	81	b	$C_{13}H_{12}ClN$	217,07	360	2
13	Br	CH3	58	86	83-86	$C_{14}H_{14}BrN$	275,03	360	2
14 17	Br	H	50	74	53	$C_{13}H_{12}BrN$	261,02	90	4
15 18	F	CH3	20	70	75-78	$C_{14}H_{14}FN$	215,11	90	4
16 19	F	H	7	78	a	$C_{13}H_{12}FN$	201,1	90	4
17	I	CH3	25	7	a	$C_{14}H_{14}IN$	323,02	360	2
18 20	I	H	8	51	a	$C_{13}H_{12}IN$	309	360	2

[a] Yellow oil, [b] Colourless liquid; Mobile Phase for Column Chromotography: Hexane: Ethyl acetate (8:2)

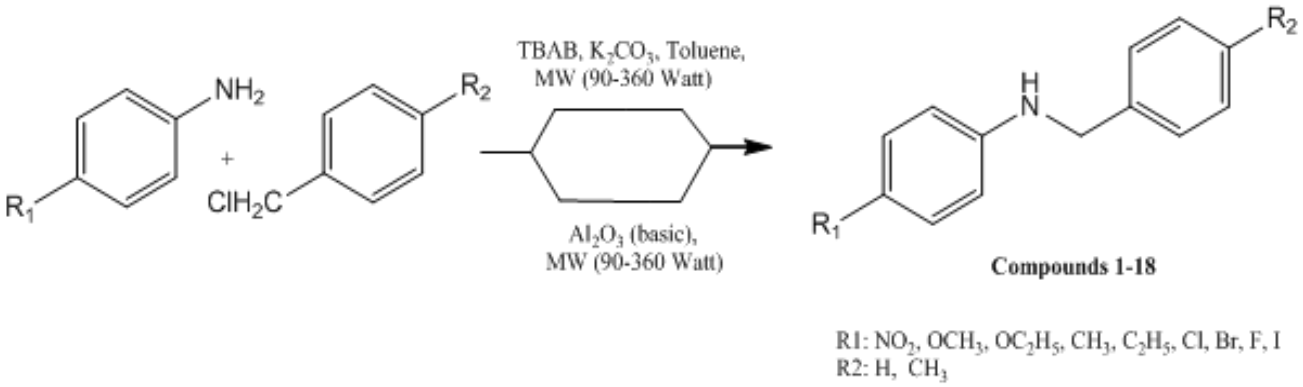
Spectroscopic data of compound 1: Yellow solid, mp 183-185°C, yield: 11%, ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.85 (d, 2H, J= 8.02 Hz), 6.75-7.05 (m, 4H), 6.44 (d, 2H), 3.98 (s, 2H, methylene) and 2.21 (s, 3H, CH_3). ^{13}C NMR (400 MHz, $CDCl_3$, ppm) 159.50, 137.21, 136.10, 135.28, 129.64, 128.56, 128.01, 127.33, 46.14, 25.56. LC-MS ES(+) m/z (M+1) 243.13.

Spectroscopic data of compound 7: White solid, mp 63-65°C, yield: 78%, ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.12-7.40 (m, 4H), 6.95 (d, 2H, J= 7.85 Hz), 6.44 (d, 2H), 4.25 (q, 2H, O-CH_2), 3.89 (s, 2H, N-CH_2), 2.34 (s, 3H, CH_3) and 1.35 (t, 3H, CH_3). ^{13}C NMR (400 MHz, $CDCl_3$, ppm) 155.40, 140.02, 136.95, 135.70, 128.87, 127.01, 115.33, 112.90, 64.61, 48.01, 21.56, 15.67. LC-MS ES(+) m/z (M+1) 242.14.

Spectroscopic data of compound 13: s White solid, yield: 86%, mp 83-86°C, ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.28 (d, 2H, J= 7.36 Hz), 6.75-7.25 (m, 4H), 6.59 (d, 2H, J= 8.11 Hz), 4.28 (s, 2H, CH_2) and 2.26 (s, 3H, CH_3). ^{13}C NMR (400 MHz, $CDCl_3$, ppm) 148.35, 137.40, 136.41, 135.01, 128.70, 128.17, 115.21, 114.30, 48.05, 21.36. LC-MS ES(+) m/z (M+1) 276.02.

Spectroscopic data of compound 17: Light green solid, yield: 25%, mp 92-95°C, ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 6.44-7.74 (m, 8H), 4.32 (s, 2H, methylene) and 2.30 (s, 3H, CH_3). ^{13}C NMR (400 MHz, $CDCl_3$, ppm) 137.40, 136.02, 135.95, 128.70, 127.87, 147.01, 114.33, 45.01, 22.56. LC-MS ES(+) m/z (M+1) 324.02.

General synthesis procedure under Solvent-Free conditions: A mixture of substituted aniline (10 mmol), benzyl chloride or p-methylbenzyl chloride (5 mmol) was mixed with Al_2O_3 (3 g), The resulting fine powder was taken in a 10 ml glass tube with a magnetic stirring bar and subjected to microwave irradiation in microwave oven, in pulses (90-360W) for a total irradiation time ranging between, 2-10 minutes. The reaction was monitored by TLC. After complete conversion, the mass was cooled to room temperature, extracted with dichloromethane (2x10 ml) and the combined organic extract was evaporated on rotary evaporator and the crude product was purified by column chromotography on silica gel with hexane: ethyl acetate (8:2) mobil phase. Synthesis pathway is shown on **Scheme 1**.



SCHEME 1: MONO AND BIS N-ALKYLATION OF PRIMARY ANILINES WITH ARYL HALIDES

RESULTS AND DISCUSSION: There are many traditional N-alkylation reactions in literature which have been performed with long reaction times and low yields. So that this study involved to develop new alternative synthetic protocols by using different microwave processing techniques. In this context, solvent-free solid supported and phase transfer catalysis conditions in microwave irradiation were used to synthesize various benzaniline compounds. Microwave assisted heating and previously reported traditional heating methods were evaluated in terms of reaction yields and times of the synthesized compounds.

Accordingly all of the compounds were synthesized successfully by using both of the microwave techniques. Substituted primary anilines and aryl halides were used in molar ratios [2:1] in order to increase the yield of the benzaniline derivatives. 18 compounds were synthesized in this work. Compounds 1, 7, 13 and 17 were synthesized and reported for the first time in this investigation. In addition, compounds 1, 3, 5, 7-9, 11, 13-18 were synthesized at first by using any microwave irradiation method. Structures were confirmed by ^{1}H-NMR, ^{13}C-NMR and mass spectras.

As a result, both of the microwave irradiation techniques significantly reduced the reaction times as they were compared with traditional synthesis methods. Particularly synthesis by solvent-free solid supported microwave heating was found more eco-friendly and had higher reaction efficiency against to phase transfer catalysis condition. It can be said that the absence of solvent clearly reduced the reaction times and generally improved the yields and there are different advantages of these solvent-free protocols as "Green Chemistry" since they provide absence of solvent thereby preventing pollution in organic synthesis.

Furthermore, this eco-friendly approach can open numerous possibilities for various N-alkylation reactions using a supported reagent on mineral oxides in future studies.

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