Microwave Irradiated Acetylation and Nitration of Aromatic Compounds

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In recent years, microwave irradiation using commercial domestic ovens has been rapidly increased to accelerate the organic reactions. It has been reported that a variety of reactions such as Diels-Alder,[1] ene,[2] Claisen reactions,[3] Fischer cyclization,[4] synthesis of heterocycles,[5] hydrolysis of esters,[6] phosphoanhydride,[7] and adenosine triphosphate,[8] hydrogenation,[9] deprotection of benzyl esters,[10] deacetylation of diacetates,[11] Graebe-Ullmann synthesis,[12] and oxazoline formation[13] could be facilitated by microwave irradiation in a good energy transferring medium. Recently we applied the microwave methodology to the Knoevenagel condensation,[14] and reported that diethyl malonate,[15] cyanoacetate[16] and several different type of aldehyde including benzaldehyde, 1-naphtaldehyde, and indol-3-carboxaldehyde were efficiently condensed within 5-15 min under microwave irradiation. Herein, we wish to report a very rapid (1-5 min) and simple acetylation and nitration reactions of various aromatic compounds by using commercial microwave oven.

The results of microwave enhanced acetylation of various aromatic alcohol and amine functional groups are summarized in Table 1. Consistently high yields (84-98%) were readily obtained without any difficulties and the reactions were usually completed within 2-5 min. Aromatic amines (entries 1 and 2) react with acetic anhydride much faster than phenol derivatives (entries 4-7). Electron withdrawing groups such as Cl and COOH did not retard the reaction rate and high yields (94-92%) were obtained within short reaction times (entries 2 and 7).

Table 1. Microwave Irradiated Acetylation Reaction of Various Aromatic Alcohol and Amine Functional Group

Entry	Substrate[a]	Product[b]	Time[c] (min)	Rf[d]	Yield[i] (%)
1	aniline	$PhNHCOCH_3$	3	0.3[e]	86
2	*p*-chloroaniline	*p*-Cl-$PhNHCOCH_3$	2	0.29[e]	94
3	*p*-phenylaniline	*p*-Ph-$PhNHCOCH_3$	2	0.16[f]	84
4	phenol	$PhOCOCH_3$	5	0.34[g]	96
5	*m*-cresol	*m*-CH_3-$PhOCOCH_3$	5	0.29[g]	97
6	*p*-cresol	*p*-CH_3-$PhOCOCH_3$	5	0.29[g]	98
7	2-hydroxy-benzoic acid	*o*-COOH-$PhOCOCH_3$	5	0.15[h]	92

[a] Purchased from Aldrich and used without further purification. [b] Purified by column chromatography. [c] The reactions were carried out in a 2450 MHz commercial microwave oven (Sam Sung, Model # RE-555 TCW). [d] Rf values were recorded by using E. Merck AG Darmstadt silica gel pf-254. [e] 5% MeOH+95% CH_2Cl_2. [f] 20% Ethyl acetate+80% Hexane. [g] 10% Ethyl acetate+90% Hexane. [h] 30% Ethyl acetate+70% Hexane. [i] Yield of isolated product.

Relatively long reflux time is usually required to carry out acetylation reaction. Our synthetic approach offers some advantages; (1) Reflux condenser is not necessary and a large vial with a loose cap or a Erlenmeyer flask with a funnel as a loose top is good enough for the reaction vessel. (2) Acetylation that normally required more than one hour can be carried out efficiently in 2-5 min in a microwave oven to afford dramatic saving in reaction time.

The results of microwave nitration reactions in mixed acid are summarized in Table 2. Halogenated substrates (entries 1 and 2) and benzyl cyanide (entry 4) gave *para*-substituted products. Cyano functional groups are often readily hydrolyzed to the corresponding carboxylic acids in acidic condition[17] and *para* substituted amide product (entry 4) was obtained under this reaction condition. Nitrobenzene and benzaldehyde gave the *meta* substituted products as expected. Aldehyde functional group was relatively inert and did not give any oxidation problem under the microwave irrdiation condition (entry 5, 65% yield).

In the case of acetanilide, *o*-nitro product was the major product presumably due to internal hydrogen bonding (entry 6). Yields were generally good to moderate (89-57%) and the reactions were complete within surprisingly short reaction time (1-3 min). Preparations of bromonitrobenzene, 1,3-dinitrobenzene were reported in 58% and 69% yield using classical nitration method[18] but our microwave method clearly represents a better yield (entries 2 and 3; 65% and 78% respectively) in shorter reaction time (1-2 min). Prolonged microwave irradiation gave no improvement in yields and only unreacted starting materials were recovered.

In conclusion, we have demonstrated a number of acetylation products can be prepared in good yields in very short reaction times under the microwave irradiation and the reaction rates of nitration can be dramatically enhanced by irradiating the reaction mixture containing nitric acid, sul-

Table 2. Microwave Irradiated Nitration Reaction of Various Aromatic Compound in Mixed Acid

Entry	Substrate[a]	Product[b]	Time[c] (min)	Rf[d]	Yield[g] (%)
1	Chlorobenzene	*p*-NO_2PhCl	2	0.25[e]	70
2	Bromobenzene	*p*-NO_2PhBr	2	0.43[e]	78
3	Nitrobenzene	*m*-NO_2PhNO_2	3	0.28[e]	76
4	Benzylcyanide	*p*-$NO_2PhCH_2CONH_2$	1	0.20[f]	89
5	Benzaldehyde	*m*-NO_2PhCHO	1	0.25[f]	65
6	Acetanilide	*o*-$NO_2PhNHCOCH_3$	1	0.22[e]	57

[a-d] Same as the footnote in Table 1. [e] 10% Ethyl acetate+90% Hexane. [f] 5% MeOH+95% CH_2Cl_2. [g] Yields were not optimized.

furic acid and various aromatic compounds in a commercial microwave oven.

Experimental Section

Melting points were taken on a Fisher-Johns melting point apparatus. Infrared spectra were recorded with a BOMEN model FT-IR M100-C15 and reported in cm^{-1}. ^1H NMR spectra were determined in *d*-chloroform solution on a FT-NMR Bruker 300 (300MHz) or FT-NMR JEOL (90 MHz), and reported in δ ppm using tetramethylsilane as an internal standard.

A typical procedure for the microwave-irradiated acetylation. In a dry vial were placed salicylic acid (1 g, 7.24 mmol, 1 equiv.) and 3.4 mL (5 equiv. 36.2 mmol) of acetic anhydride. The reaction mixture was then irradiated in a microwave oven for 5 min. The cooled mixture was quenched with 20 mL of saturated Na_2CO_3 solution and extracted with diethyl ether (30 mL). The organic layer was dried over $MgSO_4$ and concentrated. The crude product was purified by column chromatography on silica gel using ethyl acetate/hexane (30/70) as an eluent to give acetylsalicylic acid (entry 7; 1.2 g, 6.7 mmol, 92%) as a white solid. mp 136-139 °C (Lit[19] mp 138-140 °C) IR (KBr cm^{-1}) 3400-2650, 1760, 1690, 1590, 1300, 1200. ^1H NMR ($CDCl_3$): 8.15 (1H, d, *J*=7.8), 7.67 (1H, t, *J*=7.5 Hz), 7.38 (1H, t, *J*=7.6 Hz), 7.16 (1H, d, *J*=8.1 Hz). ^{13}C NMR ($CDCl_3$): 170.5, 170.2, 151.7, 134.9, 132.9, 126.5, 124.4, 122.6, 21.4.

A typical procedure for the microwave-irradiated nitration. In a dry 25 mL vial were placed 1 mL (24.9 mmol) concentrated nitric acid and 1 mL of concentrated sulfuric acid at 0 °C. The reaction mixture was treated with 1 g of mono chlorobenzene (8.9 mmol) then irradiated in a microwave oven for 2 min. The cooled mixture was poured into ice-H_2O (50 mL) and extracted with Et_2O (2×50 mL). The combined organic layers were then washed with H_2O (2×30 mL) and dried over $MgSO_4$. Removal of the volatiles in vacuo afforded the crude product which was purified by column chromatography on silica gel using ethyl acetate/hexane (10/90) as an eluent to give *p*-chloronitrobenzene (entry 1; 0.92 g, 5.9 mmol, 65.9%). mp 82-83 °C (Lit[18] 82 °C). IR (neat cm^{-1}) 3300-3150, 1600, 1510, 1340, 1080, 830. ^1H NMR ($CDCl_3$): 8.20 (2H, d, *J*=9.0 Hz), 7.55 (2H, d, *J*=9.0 Hz).

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