

PhCOCl-Py/Basic Alumina as a Versatile Reagent for Benzoylation in Solvent-Free Conditions

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Abstract: A solvent-free procedure using PhCOCl-Py/basic alumina under microwave irradiation has been developed for N-, O- and S-benzoylation.

Keywords: Benzoylation, solvent-free conditions, microwave activation, PhCOCl, basic alumina.

Introduction

Benzoylation is an important transformation in Organic Synthesis [1]. A number of reagents can be used for carrying out this reaction, such as benzoyl chloride [1], benzoic anhydride [2], benzoyltetrazole [3], 2-benzoyl-1-methylpyridinium chloride [4], S-benzoic-O,O-diethylphosphorodithioic anhydride [5], benzoyl cyanide [6], etc. Though benzoyl chloride may be a health hazard due to its toxicity, nevertheless it is widely used because of its ready availability and low cost. The reaction is usually catalyzed by bases like pyridine, triethylamine and sodium hydroxide[7].

Recently, organic reactions on solid supports [8], and those assisted by microwaves, especially under solvent-free conditions [9], have attracted much attention because of their enhanced selectivity, milder reaction conditions and associated ease of manipulation. Recently, we have reported an

acetylation using Ac_2O -py/basic alumina [10a]. Acetyl chloride did not work under these conditions, consequently development of a solvent-free protocol, meeting *Green Chemistry* principles is desirable.

Results and Discussion

For the aforementioned reasons, and in light of our general interest in using microwaves for the development of environmentally friendlier synthetic alternatives [10], we became interested in an expeditious synthesis of these compounds. We now report a simple procedure for the benzylation of amino, hydroxy and thiol groups under solvent-free conditions using PhCOCl -Py/basic alumina.

Benzylation of aniline using benzoyl chloride over different solid supports in presence of various catalysts was studied in order to select the most efficient combination (Table 1). In order to optimize the results, we also carried out benzylation of aniline under different conditions by testing various molar ratios and amounts of support. From the results it is clear that PhCOCl -Py/basic alumina was the most efficient reagent and that a ratio of 1 mmole of the substrate, 2 mmole of PhCOCl , 0.6 mmole of pyridine and 2 gm of support gave optimum results, hence we have extended the use of this reagent and conditions for the benzylation of $-\text{NH}_2$, $-\text{OH}$ and $-\text{SH}$ groups (Table 2).

Table 1. Preparation of benzanilide from aniline using various reagents (power=300 W)

Reagent	Time ^a (min)	Reaction Temp ^b (°C)	Yield (%) ^c
$\text{PhCOCl}/\text{SiO}_2$	3	62-64	89
$\text{PhCOCl}/\text{K10}$	8	59-61	71
$\text{PhCOCl}/p\text{-TsOH}/\text{SiO}_2$	10	39-41	48
$\text{PhCOCl}/\text{Acidic Al}_2\text{O}_3$	8	52-54	64
$\text{PhCOCl}/\text{TFA}/\text{SiO}_2$	10	51-53	45
$\text{PhCOCl}/\text{H}_2\text{SO}_4/\text{SiO}_2$	4	52-54	84
$\text{PhCOCl}/\text{DMSO}/\text{SiO}_2$	2	50-52	77
PhCOCl-Py/Basic Al_2O_3	1	92-94	100

Notes: ^a Time at which maximum yield was obtained.

^b Final temperature was measured by immersing a glass thermometer into the reaction mixture at the end of exposure to microwave irradiation and gives the approximate temperature range.

^c Yield of isolated products.

Further, the support can be reused several times without loss of activity. The method is environmentally friendly as hydrochloric acid (the by-product) remains adsorbed on the basic alumina and does not escape into the atmosphere. The method can be used for selective mono and dibenzylation (cf. Table 2, entries 19, 20, 21, 22 and 33, 34).

Table 2. Microwave-assisted N-, O- and S-benzoylations using PhCOCl-Py/basic alumina (power = 300W).

Entry	Reactant	Product	Temperature ^a (°C)	Time (min)	Yield ^b (%)	m.p./Lit. m.p. (°C)
1	Aniline	Benzanilide	92-94	1	100	162-3/164-6 [11]
2	2-Nitroaniline	2-Nitrobenzanilide	85-87	2	87	96-7/98 [12]
3	3-Nitroaniline	3-Nitrobenzanilide	94-96	5	60	155-6/157 [12]
4	4-Nitroaniline	4-Nitrobenzanilide	99-100	6	92	198-9/199 [12]
5	2-Anisidine	2-Methoxybenzanilide	134-36	3	60	58-59/60 [12]
6	4-Anisidine	4-Methoxybenzanilide	100-02	2	65	153-54/154 [12]
7	3-Toluidine	3-Methylbenzanilide	84-86	1	94	124-5/125 [12]
8	4-Toluidine	4-Methylbenzanilide	84-86	2	55	156-7/158 [12]
9	Piperazine	N-Benzoylpiperazine	94-96	1	55	194-5/196 [12]
10	Piperidine	N-Benzoylpiperidine	91-93	1.5	70	317/320-21 [13] ^c
11	Morpholine	N-Benzoylmorpholine	103-05	2	64	73-4/74-5 [13]
12	Benzylamine	N-Benzoylbenzylamine	104-06	1	93	104-5/105-6 [13]
13	Cyclohexylamine	N-Benzoylcyclohexyl- amine	96-98	1	79	145-6/147 [12]
14	Phenol	Phenylbenzoate	109-11	4	74	68-9/69-72 [11]
15	3-Cresol	3-Methylphenyl-benzoate	128-30	6	70	52-53/55 [11]
16	4-Cresol	4-Methylphenylbenzoate	98-100	5	71	70-71/71 [11]
17	4-Hydroxybenzoic acid	4-Benzoyloxybenzoic acid	81-83	3	69	220-21/221-23 [13]
18	Vanillin	4-Benzoyloxy-3-methoxy benzaldehyde	97-99	4	64	77-78/78 [12]
19	Resorcinol	3-Hydroxyphenyl- benzoate	41-43	9	65	134/135-7 [13]
20	Resorcinol	1,3-Dibenzoyloxy- benzene	92-94	9	55	115-17/117 [13]
21	Resacetophenone	4-Benzoyloxy-2-Hydroxy- acetophenone	74-76	7	59	105-6/106-7 [13]
22	Resacetophenone	2,4-Dibenzoyloxyaceto phenone	78-80	8	65	78-9/80-1 [13]
23	2-Nitrophenol	2-Nitrophenylbenzoate	98-100	7	60	49-50/50 [12]
24	4-Nitrophenol	4-Nitrophenylbenzoate	74-76	6	65	139-40/142 [12]
25	1-Naphthol	1-Benzoyloxy- naphthalene	108-10	4	62	54-5/56 [12]

Table 2. (cont.)

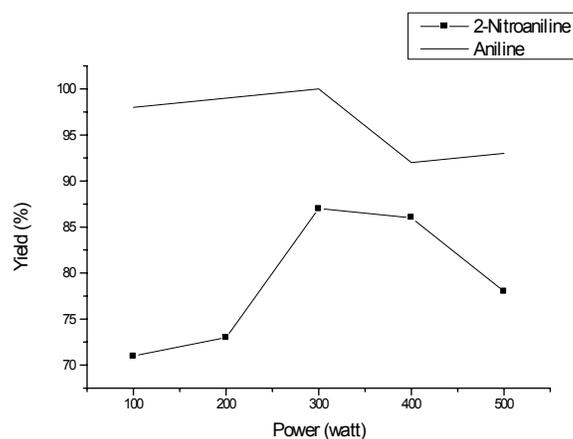
Entry	Reactant	Product	Temperature ^a (°C)	Time (min)	Yield ^b (%)	m.p./Lit. m.p. (°C)
26	2-Naphthol	2-Benzoyloxy-naphthalene	104-06	2	60	105-06/107 [12]
27	Ethylenediamine	N,N-Dibenzoylethylenediamine	112-14	2	39	242-43/244 [13]
28	2-Amino-4-phenylthiazole	2-(N-Benzoylamino)-4-phenylthiazole	113-15	3	72	156-57
29	2-Amino-4-(4-bromophenyl)thiazole	2-(N-Benzoylamino)-4-(4-bromophenyl)thiazole	81-83	2	99	115-16
30	2-Amino-4-(4-chlorophenyl)thiazole	2-(N-Benzoylamino)-4-(4-chlorophenyl)thiazole	115-17	2	65	156-57
31	2-Amino-4-(4-fluorophenyl)thiazole	2-(N-Benzoylamino)-4-(4-fluorophenyl)thiazole	119-21	10	98	123-24
32	2-Aminobenzenthio	1-Thiobenzoyloxy-2-aminobenzene	62-64	5	97	115-16
33	2-Aminobenzenthio	1-Thiobenzoyloxy-2-N-benzoylamino	98-100	2	60	153-4/154-5 [13]

Notes: ^a Final temperature was measured by immersing a glass thermometer in the reaction mixture at the end of the exposure to microwave irradiation and gives an approximate temperature range.

^b Yield of isolated products

^c Boiling point

Figure 1. Effect of microwave power on the benzylation of aniline and 2-nitroaniline



Further, the reaction has been carried out at different power levels from 80-800 watts in the cases of aniline and 2-nitroaniline in order to select the more appropriate power level. The results are shown graphically in Figure 1. It is clear that power level of 300 W gave the maximum yield.

Conclusions

A rapid, economic and environmentally friendly method has been developed for benzylation of -NH₂, -OH and -SH groups using PhCOCl-Py/basic alumina. The reagent system described here may be a good alternative to well known methods since the benzylation proceeds expeditiously with high yields under solvent-free conditions.

Experimental

General

Melting points were recorded on a Toshniwal melting point apparatus and are uncorrected. All reactions were carried out in a commercially available BPL BMO 800T domestic microwave oven having a maximum power output of 800 W operating at 2450 MHz. IR spectra were obtained on a Hitachi 270-30 spectrophotometer using KBr discs. ¹H-NMR spectra were recorded using a JNM-PMX 60 NMR Spectrometer (60 MHz). Mass spectra were recorded using JEOL D-300 spectrometer.

General Synthetic Procedure

Substrate (2 mmole), benzoyl chloride (4 mmole), pyridine (0.6 mmole) and basic alumina (2 g) were added in a 50 mL beaker. The mixture was stirred to obtain a free flowing powder, which was irradiated in a microwave oven at 300 W for an appropriate time (Table 2, as monitored by TLC). After cooling to room temperature, the product was extracted with methylene chloride (3 x15 mL). The combined extracts were washed with water and dried over sodium sulfate. The product obtained after removal of solvent under reduced pressure was crystallized from a suitable solvent (EtOAc-pet. ether; EtOH). The structure of the products was confirmed by ¹H-NMR, IR and mass spectral data and comparison with authentic samples prepared according to literature methods.

Spectral and Analytical Data of Selected Compounds

2-(N-Benzoylamino)-4-phenylthiazole (entry **28**): IR cm⁻¹: 1586 (C=N), 1720 (COPh); ¹H-NMR (CDCl₃+ DMSO-*d*₆): δ 5.06 (bs, 1H, NH, exchangeable with D₂O), 7.1-7.8 (m, 11H, H_{arom}); m/z(%): M⁺ 280 (77.5); Anal. calcd. for C₁₆H₁₂N₂OS: C, 68.57; H, 4.28; N, 10.00. Found: C, 68.53; H, 4.25; N, 9.98.

2-(*N*-Benzoylamino)-4-(4-bromophenyl)thiazole (entry 29): IR cm^{-1} : 1590 (C=N), 1722 (COPh); $^1\text{H-NMR}$ ($\text{CDCl}_3 + \text{DMSO-}d_6$): δ 4.95 (bs, 1H, NH, exchangeable with D_2O), 7.06-8.0 (m, 10H, H_{arom}); $m/z(\%)$: M^+ 359 (40.2); Anal. calcd. for $\text{C}_{16}\text{H}_{11}\text{BrN}_2\text{OS}$: C, 53.48; H, 3.06; N, 7.79. Found: C, 53.43; H, 3.02; N, 7.75.

2-(*N*-Benzoylamino)-4-(4-chlorophenyl)thiazole (entry 30): IR cm^{-1} : 1582 (C=N), 1720 (COPh); $^1\text{H-NMR}$ ($\text{CDCl}_3 + \text{DMSO-}d_6$): δ 4.89 (bs, 1H, NH, exchangeable with D_2O), 7.26-8.5 (m, 10H, H_{arom}); $m/z(\%)$: M^+ 314 (37.5); Anal. calcd. for $\text{C}_{16}\text{H}_{11}\text{ClN}_2\text{OS}$: C, 61.04; H, 3.49; N, 8.90. Found: C, 61.07; H, 3.43; N, 8.95.

2-(*N*-Benzoylamino)-4-(4-fluorophenyl)thiazole (entry 31): IR cm^{-1} : 1596 (C=N), 1730 (COPh); $^1\text{H-NMR}$ ($\text{CDCl}_3 + \text{DMSO-}d_6$): δ 5.41 (bs, 1H, NH, exchangeable with D_2O), 7.1-8.6 (m, 10H, H_{arom}); $m/z(\%)$: M^+ 298 (53.1); Anal. calcd. for $\text{C}_{16}\text{H}_{11}\text{FN}_2\text{OS}$: C, 64.42; H, 3.69; N, 9.39. Found: C, 64.39; H, 3.75; N, 9.33.

1-Thiobenzoyloxy-2-aminobenzene (entry 32): IR cm^{-1} : 3300, 3469 (NH_2), 1730 (COPh); $^1\text{H-NMR}$ ($\text{CDCl}_3 + \text{DMSO-}d_6$): δ 7.1-8.5 (m, 9H, H_{arom}), 9.16 (bs, 2H, NH_2 , exchangeable with D_2O); $m/z(\%)$: M^+ 229 (53.1); Anal. calcd. for $\text{C}_{13}\text{H}_{11}\text{NOS}$: C, 68.12; H, 4.80; N, 6.11. Found: C, 68.09; H, 4.75; N, 6.08.

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