p-Toluene sulfonic acid-catalysed microwave synthesis of symmetrical bisamides by reaction between aromatic aldehydes and amides

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Reaction between aldehydes and amides catalysed by *p*-toluene sulfonic acid in microwave conditions provided a simple and efficient one-pot route for the synthesis of symmetrical bisamide derivatives in excellent yields.

Keywords: bisamides, *p*-toluene sulfonic acid, aldehydes, amides

Bisamides are useful synthetic intermediates. Pyrolysis of benzylidenebisbenzamides afforded *N*-benzoylbenzaldimine derivatives, which has been used for the synthesis of *N*-(α-alk oxybenzy1)benzamides.[1] Bisamides are also important fragments for the introduction of *gem*-diaminoalkyl residues *in retro-in verso* pseudopeptide derivatives[2] by treating the corresponding amide with iodobenzene bistrifluoroacetate.[3,4] Previously reported methods to prepare bisamides all applied the reaction of the corresponding amides with aldehydes in solution in the presence of strong acidic catalysts such as triflic acid.[5] Recently we reported the reaction of aldehydes with alkyl nitriles promoted by chlorosulfonic acid[6] and the reaction between aldehydes and amides under solvent-free conditioin affording symmetrical bisamides[7].

Table 1 Acid catalysed one-pot condensation reaction between 4-chlorobenzaldehyde and acetamide

Entry	Catalyst	Catalyst /mol%	Temperature /°C	Time /min	Yield[a] /%
1	NH_4Cl	10	100	120	50
2	$ZrCl_4$	10	100	120	65
3	$FeCl_3.3H_2O$	10	100	120	77
4	$ZnCl_2$	10	100	120	85
5	*p*-TSA	10	100	60	95
6	*p*-TSA	1	100	120	97
7	*p*-TSA	5	100	60	95
8	*p*-TSA	20	100	120	85
9	*p*-TSA	10	70	120	85

[a] Isolated yield.

Results and discussion

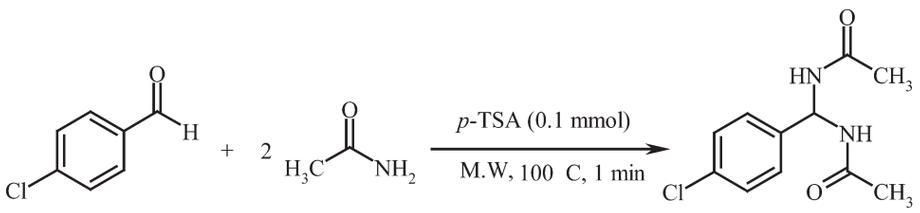
We describe here a practical and inexpensive method for the preparation of symmetrical bisamides via a three-component condensation reaction between aldehydes and amides under microwave conditioin.

Initially, we studied the reaction of benzaldehyde and acetamide using different catalysts under microwave conditions at 100 °C, and the results are listed in Table 1 (Scheme 1). *p*-TSA was found to show better catalytic activity among these catalysts. When *p*-TSA was used, the reaction was completed after 1min (the reaction progress was monitored by TLC) and *N*-[acetylamino phenyl methyl]-acetamide **3a** was obtained in 95% yield (Table 1, entry 5). Moreover, we found that the yields were obviously affected by the amount of *p*-TSA loaded. When 1 mol %, 5 mol %, 10 mol %, and 20 mol % of *p*-TSA were used, the yields were 20%, 77%, 95%, and 95%, respectively (Table 1, entries 5–8). Therefore, 10 mol % of *p*-TSA was sufficient and excessive amount of catalyst did not increase the yields significantly (Table 1, entry 8). In addition, no product was detected in the absence of the catalyst. Furthermore, it was found that increasing the reaction time over 60 min or reaction temperature over 100 °C did not improve the yields.

The above reaction was also examined in various solvents (Table 2). The results indicated that different solvents affected the efficiency of the reaction. Acetone, dichloromethane, THF, and chloroform afforded moderate yields (Table 2, entries 1–4), while when 1,2-dichloroethane and toluene were used as solvents, better results were obtained (Table 2, entries 5 and 6). However, the best result was obtained when the reaction was carried out under solvent-free conditions at 100 °C (Table 2, entry 7).

To study the scope of the reaction, a series of aldehydes and amides were applied. The results are shown in Table 3. In all cases, aromatic aldehydes substituted with either electron-donating or electron-withdrawing groups underwent the reaction smoothly and gave the products in good yields. It could also be concluded that the aldehydes bearing electron-withdrawing groups required shorter time and gave higher yields (Table 3). In addition, aromatic aldehydes reacted with other amides, such as propionamide (Table 3, entries 8–14) and benzamide (Table 3, entries 17 and 18) to afford the corresponding bisamide derivatives in excellent yields. The reaction is also compatible with aliphatic aldehyde (possessing α-hydrogen), so that 2-phenyl-propion aldehyde and 3-phenylpropenal reacted with amides affording the related bisamides in good yields (Table 3, entries 13 and 19)

Compounds **3a–y** were known and their structures were deduced by comparison of melting points and spectral data with authentic samples.[5–7] The structure of other products were



Scheme 1 Reaction between 4-chlorobenzaldehyde and acetamide catalysed by *p*-TSA

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Table 2 Solvent effect on the reaction between 4-chlorobenzaldehyde (1 equiv) and acetamide(1.1 equiv) catalysed by *p*-TSA (0.1 equiv)

Entry	Solvent	Temperature /°C	Time /min	Yield* /%
1	Acetone	Reflux	180	60
2	Dichloromethane	Reflux	180	65
3	THF	Reflux	180	65
4	Chloroform	Reflux	180	43
5	1,2-Dichloroethane	Reflux	180	80
6	Toluene	Reflux	180	75
7	Neat	100	60	95

proved on the basis of the mass spectrometry and ^{1}H and ^{13}C NMR spectra. For example, the ^{1}H NMR spectrum of compound **3z** exhibited a triplet ($^{3}J_{HH}$ = 8 H_Z) at 6.99 ppm for methine group proton, a multiplet at 7.39–7.91 ppm for aromatic protons and a doublet ($^{3}J_{HH}$ = 8 H_Z) at 9.05 ppm for NH protons. The phenyl groups of each amide group are diastereotopic and two signals were observed for them at 20.1 and 20.4 ppm in the ^{13}C NMR spectrum of compound **3z**. Methine group carbon resonated at 59.3 ppm. Twelve signals were observed between 128.3 and 140.1 ppm for aromatic carbons and two carbonyl carbons were observed at 166.6 and 168.8 ppm.

In conclusion, we have developed a highly efficient synthesis of symetrical bisamide derivatives from aldehydes and amides under microwave conditions. The advantages of the reported method are inexpensive and easily available starting materials, simple reaction conditions, high yields, single-product reaction and simple workup procedure.

Experimental

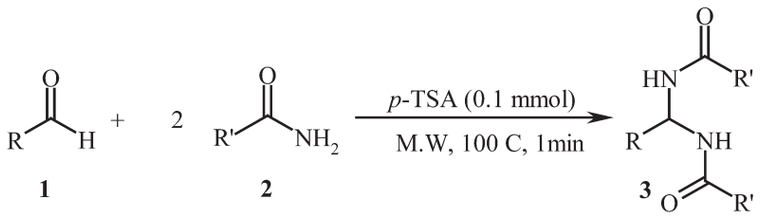
Melting points were determined with an electrothermal 9100 apparatus. Elemental analyses were performed at the analytical laboratory of Science and Researchs Unite of Islamic Azad University. Mass spectra were recorded on a FINNIGAN-MAT 8430 mass spectrometer operating at an ionisation potential of 70 eV. IR spectra were recorded on a Shimadzu IR-470 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on Bruker DRX-250 Avance spectrometer at solution in d_6-DMSO using TMS as internal standard. The chemicals used in this work were purchased from Fluka (Buchs, Switzerland) and were used without further purification.

General procedure:

To a stirred mixture of the amide (2.2 mmol) and aldehyde (1.0 mmol) in a round-bottomed flask equipped with condenser at 100 °C was added *p*-TSA (0.1 mmol) and the reaction was heated for the given time. For microwave-assisted reactions the above premixed mixture was irradiated at 475 W in a domestic microwave oven. The progress of reaction was followed by TLC. After completion of the reaction, ethyl acetate (10 mL) was added to the resulting mixture and the product was filtered off and washed with ethyl acetate (10 mL).

N-[benzoylamino(4-clorophenyl)methyl]-benzamide (**3z**): White powder; m.p. 246–248 °C. IR (KBr) (ν_{max}, cm^{-1}): 3255 (NH), 1648 (C=O). MS (*m/z*, %): 364 (M^+,4). ^{1}H NMR (500 MHz, d_6-DMSO): δ 6.99 (1 H, t ,$^{3}J_{HH}$ = 8 Hz, CH), 9.05 (2 H, d, $^{3}J_{HH}$ = 8 H_Z, 2 NH). 7.39–

Table 3 Three-component reaction of aldehydes and amides catalysed by p-TSA



Entry	R	R'	Yield/%*	M.p.	
				Found	Reported (Lit.)
1	4-BrC_6H_4	Me	90	244–247	246–248
2	3-$NO_2C_6H_4$	Me	94	232–234	231–233
3	4-$NO_2C_6H_4$	Me	96	272–274	270–272
4	4-ClC_6H_4	Me	91	261–262	258–260
5	2-$NO_2C_6H_4$	Me	91	238–240	237–239
6	4-$CH_3C_6H_4$	Me	84	271–273	269–271
7	2-Cl-5-$NO_2C_6H_3$	Me	90	265–267	266–268
8	4-$NO_2C_6H_4$	Et	91	246–248	244–246
9	3-$NO_2C_6H_4$	Et	93	157–159	155–157
10	4-ClC_6H_4	Et	94	142–144	143–145
11	4-BrC_6H_4	Et	91	160–162	162–164
12	4-ClC_6H_4	iso-Pro	90	244–245	241–243
13	$C_6H_5CHCH_3$	Et	88	186–188	189–192
14	3-$MeOC_6H_4$	Et	91	175–177	178–180
15	2-$MeOC_6H_4$	Me	92	226–229	225–228
16	4-$MeOC_6H_4$	Me	90	224–226	221–223
17	3-$MeOC_6H_4$	Ph	90	186–188	188–190
18	3-$O_2NC_6H_4$	Ph	92	193–195	190–192
19	C_6H_4CHCH	Me	86	192–194	195–197
20	$PhCH_2CH_2$	Me	98	203–204	206–207
21	$PhCH_2CH_2$	Et	92	195–197	198–199
22	$PhCH_2CH_2$	Ph	91	241–243	244–245
23	Ph	Me	89	238–240	242
24	4-$MeOC_6H_4$	Me	68	226–228	230–231
25	4-$NO_2C_6H_4$	Ph	91	230–232	234–236
26	4-ClC_6H_4	Ph	93	246–248	–

*Isolated yields

7.91 (1 H, m,14 CH aromatic). ^{13}C NMR (125.75 MHz, d_6-DMSO): δ 59.3 (CH), 128.3, 128.4, 129.1, 129.2 (aromatic carbons of aldehyde moiety), 129.1, 129.3, 132.0, 132.5, 133.1, 134.6, 135.1 and 140.1 (carbons of two phenyl rings), 166.6, 168.8 (2C=O). Analyses: Calcd for $C_{21}H_{17}ClN_2O_2$: C, 69.14; H, 4.70; N, 7.68. Found: C, 69.3; H, 4.6; N, 7.5%.

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