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p-TOLUENE SULFONIC ACID–CATALYZED, SOLVENT-FREE SYNTHESIS OF SYMMETRICAL BISAMIDES BY REACTION BETWEEN ALDEHYDES AND AMIDES

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

Keywords: Aldehydes; amides; bisamides; *p*-toluene sulfonic acid; solvent-free reaction

Bisamides are important fragments for the introduction of *gem*-diaminoalkyl residues in retro-inverso pseudo-peptide derivatives[1] by treating the corresponding amide with iodobenzene bistrifluoroacetate.[2,3] Bisamides are also useful synthetic intermediates. Pyrolysis of benzylidenebisbenzamides afforded *N*-benzoylbenzaldimine derivatives, which have been used for the synthesis of *N*-(α-alkoxybenzy1)benzamides.[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, which afforded symmetrical bisamides.[6] This reaction can only be applied for electron-deficient aldehydes. We herein describe a practical and inexpensive method for the preparation of symmetrical bisamides via a three-component condensation reaction between aldehydes and amides under solvent-free conditions.

Initially, we studied the reaction of 4-bromobenzaldehyde and acetamide using different catalysts under solvent-free condition at 100 °C (Scheme 1), and the results are listed in Table 1. *p*-Toluene sulfonic acid (*p*-TSA) showed the best catalytic activity among these catalysts. When *p*-TSA was used, the reaction was completed after 1 h (the reaction progress was monitored by thin-layer chromatography, TLC), and *N*-[acetylamino (4-bromophenyl) 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, 5, 10, and 20 mol% of *p*-TSA

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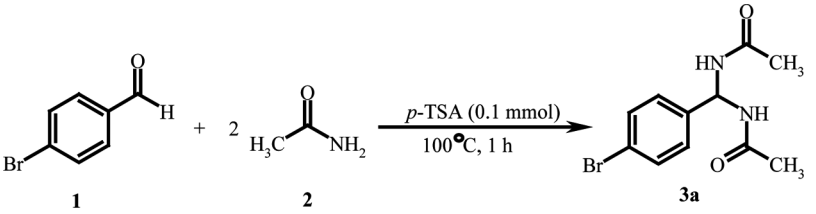


1 2 3a

Scheme 1. Reaction between 4-bromobenzaldehyde and acetamide catalyzed by *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 an 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.

This reaction was also examined in various solvents (Table 2). The results indicated that different solvents affected the efficiency of the reaction. Acetone, dichloromethane, tetrahydrofuran (THF), and chloroform afforded moderate yields (Table 2, entries 1–4), whereas when 1,2-dichloroethane and toluene were used as solvents, better results were obtained (Table 2, entries 5, 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 gave greater yields (Table 3). In addition, aromatic aldehydes reacted with other amides, such as propionamide (Table 3, entries 13–19) and benzamide (Table 3, entries 20–23) to afford the corresponding bisamide derivatives in excellent yields. The reaction is also compatible with aliphatic aldehydes (aldehydes possessing α-hydrogen), so that 2-phenylpropionaldehyde reacted with amides, affording the related bisamides in good yields

Table 1. Acid-catalyzed one-pot condensation reaction between 4-bromobenzaldehyde and acetamide[a]

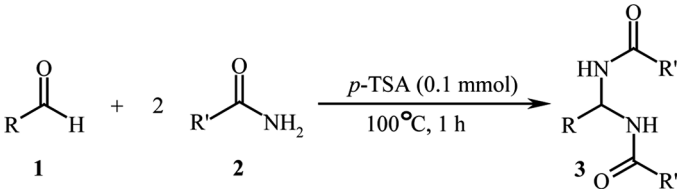
Entry	Catalyst	Catalyst (mol%)	Temperature (°C)	Time (min)	Yield[b] (%)
1	NH_4Cl	10	100	120	50
2	$ZrCl_4$	10	100	120	65
3	$FeCl_3 \cdot 3H_2O$	10	100	120	77
4	$ZnCl_2$	10	100	120	85
5	*p*-TSA	1	100	60	20
6	*p*-TSA	5	100	60	77
7	*p*-TSA	10	100	60	95
8	*p*-TSA	20	100	60	95
9	*p*-TSA	10	70	120	85

[a]Reaction conditions: 4-bromobenzaldehyde (1.0 mmol), acetamide (2.2 mmol), neat, 100 °C.
[b]Isolated yield.

Table 2. Solvent effect on the reaction between 4-bromobenzaldehyde (1 eq) and acetamide (2.2 eq) catalyzed by *p*-TSA (0.1 eq)

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

Table 3. Three-component reaction of aldehydes and amides catalyzed by *p*-TSA



					Mp	
Entry	R	R′	Product	Yield%[a]	Found	Reported (Lit.)
1	4-BrC_6H_4	Me	**3a**	91	244–246	246–248[6]
2	3-$NO_2C_6H_4$	Me	**3b**	93	230–232	231–233[6]
3	4-$NO_2C_6H_4$	Me	**3c**	95	271–273	270–272[6]
4	4-ClC_6H_4	Me	**3d**	92	260–262	258–260[6]
5	2-$NO_2C_6H_4$	Me	**3e**	92	238–240	237–239[6]
6	4-$CH_3C_6H_4$	Me	**3f**	85	270–272	269–271[6]
7	2-Cl-5-$NO_2C_6H_3$	Me	**3g**	91	265–267	266–268[6]
8	2-$MeOC_6H_4$	Me	**3h**	90	225–228	—
9	4-$MeOC_6H_4$	Me	**3i**	91	221–223	221–222[5]
10	C_6H_4CHCH	Me	**3j**	87	195–197	—
11	$PhCH_2CH_2$	Me	**3k**	99	202–203	202–203[5]
12	Ph	Me	**3l**	90	239–240	239–240[5]
13	4-$NO_2C_6H_4$	Et	**3m**	90	245–247	244–246[6]
14	4-BrC_6H_4	Et	**3n**	90	160–162	162–164[6]
15	3-$NO_2C_6H_4$	Et	**3o**	92	157–159	155–157[6]
16	$C_6H_5CHCH_3$	Et	**3p**	89	189–192	—
17	3-$MeOC_6H_4$	Et	**3q**	92	178–180	—
18	4-ClC_6H_4	Et	**3r**	93	145–147	143–145[6]
19	$PhCH_2CH_2$	Et	**3s**	94	180–182	178–179[5]
20	$PhCH_2CH_2$	Ph	**3t**	93	247–249	248–249[5]
21	3-$MeOC_6H_4$	Ph	**3u**	90	188–190	—
22	3-$NO_2C_6H_4$	Ph	**3v**	93	190–192	—
23	4-$NO_2C_6H_4$	Ph	**3w**	90	265–267	265–267[5]
24	4-ClC_6H_4	iso-Propyl	**3x**	90	243–245	241–243[6]

[a]Isolated yield.

(Table 3, entries 19, 20). Cinamaldehyde also reacted with acetamide under similar conditions to afford bisamide **3j** in good yield (Table 3, entry 10).

Compounds **3h, 3j, 3p, 3q, 3u,** and **3v** were new, and their structures were deduced by elemental and spectral analysis. Other products were known, and their structures were deduced by comparison of melting points and spectral data with authentic samples.[5,6] The ^{1}H NMR spectrum of compound **3p** exhibited a doublet at 1.78 ppm ($^{3}J_{HH} = 7$ Hz) for methyl of aldehyde moiety, a multiplet at 3.14 ppm and a quartet ($^{3}J_{HH} = 7$ Hz) at 5.48 ppm for two CH groups, and multiplets at 7.13–7.28 ppm for aromatic protons. Two propionamido groups are diastereotopic and showed distinct signals at NMR spectra of compound **3p**. Two triplets ($^{3}J_{HH} = 7$ Hz) at 0.75 and 0.98 ppm and two quartets at 1.82 and 2.09 ppm were observed for two ethyl groups protons. Two NH protons resonated as two doublets ($^{3}J_{HH} = 8$ Hz) at 7.78 and 7.96 ppm. ^{13}C NMR spectrum of compound **3p** showed 13 distinct signals, consistent with the proposed structure. The infrared (IR) spectrum of compound **3p** showed strong absorption bands at 3300 and 1658 cm^{-1} for NH and carbonyl groups, respectively.

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

EXPERIMENTAL

General

Melting points were determined with an electrothermal 9100 apparatus. Elemental analyses were performed using a Costech ECS 4010 CHNS-O analyzer at the analytical laboratory of Islamic Azad University, Yazd Branch. Mass spectra were recorded on a Finnigan-MAT 8430 mass spectrometer operating at an ionization 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 dimethyl sulfoxide (d_6-DMSO) using tetramethylsilane (TMS) as internal standard. The chemicals used in this work purchased from Fluka (Buchs, Switzerland) and were used without further purification.

General Procedure for the Preparation of Bisamides 3a–x

A mixture of amide (2.2 mmol), aldehyde (1.0 mmol), and *p*-TSA (0.1 mmol) was stirred in an oil bath at 100 °C, and the reaction was followed by TLC. After completion of the reaction, ethyl acetate (10 mL) was added to the reaction mixture and the product was filtered off and washed with ethyl acetate (10 mL).

Selected Data

***N*-[Acetylamino(2-methoxyphenyl)methyl]-acetamide (3h).** White powder; mp 225–228 °C. IR (KBr) (ν_{max}, cm^{-1}): 3285 (NH), 1683 (C=O). MS (m/z, %): 236

(M^+, 8). ^{1}H NMR (250 MHz, d_6-DMSO): δ 1.80 (6 H, s, 2 CH_3), 3.77 (3 H, s, OCH_3), 6.66 (1 H, t $J = 8$ Hz, CH), 6.90–7.34 (4 H, m, aromatic), 8.30 (2 H, d $J = 8$ Hz, 2 NH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 21.9 (2 CH_3), 52.8 (OCH_3), 55.0 (CH), 110.5, 119.4, 126.5, 127.8, 128.4 and 156.0 (aromatic), 167.7 (2 C=O). Analyses: Calcd. for $C_{12}H_{16}N_2O_3$: C, 61.00; H, 6.83; N, 11.86. Found: C, 61.1; H, 6.9; N, 11.7.

***N*-[Acetylamino(4-methoxyphenyl)methyl]-acetamide (3i).** White powder; mp 221–223 °C. IR (KBr) (ν_{max}, cm^{-1}): 3270 (NH), 1686 (C=O). MS (m/z, %): 236 (M^+, 9). ^{1}H NMR (250 MHz, d_6-DMSO): δ 1.84 (6 H, s, 2 CH_3), 3.73 (3 H, s, OCH_3), 6.45 (1 H, t $J = 8$ Hz, CH), 6.89 and 7.24 (4 H, 2 d $J = 8$ Hz, aromatic), 8.43 (2 H, d $J = 8$ Hz, 2 NH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 21.9 (2 CH_3), 54.6 (OCH_3), 56.3 (CH), 113.0, 127.0, 132.0 and 158.1 (aromatic), 167.9 (2 C=O). Analyses: Calcd. for $C_{12}H_{16}N_2O_3$: C, 61.00; H, 6.83; N, 11.86. Found: C, 61.1; H, 6.9; N, 11.7.

***N*-(1-Acetylamino-3-phenyl-allyl)-acetamide (3j).** White powder; mp 195–197 °C. IR (KBr) (ν_{max}, cm^{-1}): 3275 (NH), 1666 (C=O). MS (m/z, %): 232 (M^+, 7). ^{1}H NMR (250 MHz, d_6-DMSO): δ 1.86 (6 H, s, 2 CH_3), 6.03 (1 H, m, CH), 6.28 (1 H, dd $J = 5$ Hz, $J = 15$ Hz, olefinic CH), 6.56 (1 H, d $J = 15$ Hz, olefinic CH), 7.23–7.45 (5 H, m, aromatic), 8.37 (2 H, d $J = 8$ Hz, 2 NH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 22.0 (2 CH_3), 55.4 (CH), 125.8, 127.3, 128.1, 129.3 and 135.5 (aromatic and olefinic carbons), 167.9 (2 C=O). Analyses: Calcd. for $C_{13}H_{16}N_2O_2$: C, 67.22; H, 6.94; N, 12.06. Found: C, 67.3; H, 6.8; N, 12.1.

***N*-(3-Phenyl-1-propionylamino-propyl)-propionamide (3p).** White powder; mp 189–192 °C. IR (KBr) (ν_{max}, cm^{-1}): 3300 (NH), 1658 (C=O). MS (m/z, %): 262 (M^+, 8). ^{1}H NMR (250 MHz, d_6-DMSO): δ 0.75 and 0.98 (6 H, 2 t $J = 8$ Hz, 2 CH_3), 1.78 (3 H, d $J = 7$ Hz, CH_3), 1.82 and 2.09 (4 H, 2 p $J = 8$ Hz, 2 CH_2), 3.14 (1 H, m, CH), 5.48 (1 H, q $J = 8$ Hz, CH), 7.13–7.28 (5 H, m, aromatic), 7.78 and 7.96 (2 H, 2 d $J = 8$ Hz, 2 NH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 9.1, 9.3 and 17.2 (3 CH_3), 27.8 and 27.9 (2 CH_2), 42.4 and 58.9 (2 CH), 125.6, 127.1, 127.4 and 142.9 (aromatic), 171.3 and 171.9 (2 C=O). Analyses: Calcd. for $C_{15}H_{22}N_2O_2$: C, 68.67; H, 8.45; N, 10.68. Found: C, 68.8; H, 8.5; N, 10.6.

***N*-[Propionylamino(3-methoxyphenyl)methyl]-propionamide (3q).** White powder; mp 178–180 °C. IR (KBr) (ν_{max}, cm^{-1}): 3280 (NH), 1660 (C=O). MS (m/z, %): 618 (M^+, 9). ^{1}H NMR (250 MHz, d_6-DMSO): δ 0.99 (3 H, t $J = 8$ Hz, CH_3), 2.15 (2 H, q $J = 8$ Hz, CH_2), 6.51 (1 H, t $J = 8$ Hz, CH), 6.86 (1 H, s, CH aromatic), 7.13 and 7.49 (2 H, 2 d $J = 8$ Hz, 2 CH aromatic), 7.28 (1 H, t $J = 8$ Hz, Hz, CH aromatic), 8.39 (2 H, d, $J = 8$ Hz, 2 NH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 9.2 and 9.3 (CH_3), 27.9 (CH_2), 54.5 (OCH_3), 58.1 (CH), 112.1 112.4 119.3, 128.9, 132.7, 158.9 (aromatic), 170.1 (C=O). Analyses: Calcd. for $C_{14}H_{20}N_2O_3$: C, 63.62; H, 7.63; N, 10.60. Found: C, 63.5; H, 7.7; N, 10.5.

***N*-[Benzoylamino(3-methoxyphenyl)methyl]-benzamide (3u).** White powder; mp 188–190 °C. IR (KBr) (ν_{max}, cm^{-1}): 3280 (NH), 1646 (C=O). MS (m/z, %): 360 (M^+, 5). ^{1}H NMR (250 MHz, d_6-DMSO): δ 6.89 (1 H, t $J = 8$ Hz, CH), 7.05 (3 H, m, 3 CH aromatic), 7.31 (1 H, t $J = 8$ Hz, CH aromatic), 7.53 (6 H, m,

6 CH aromatic), 7.91 (4 H, d $J = 8$ Hz, 4 CH aromatic), 9.04 (2 H, d, $J = 8$ Hz, 2 NH).. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 54.5 (OCH_3), 58.1 (CH), 111.9 112.3 118.3, 128.9, 133.3, 158.8 (aromatic carbons of aldehyde moiety), 127.0, 127.8, 131.0 and 141.4 (carbons of two phenyl rings), 165.1 (C=O). Analyses: Calcd. for $C_{22}H_{20}N_2O_3$: C, 73.32; H, 5.59; N, 7.77. Found: C, 73.4; H, 5.7; N, 7.6.

***N*-[Benzoylamino(3-nitrophenyl)methyl]-benzamide (3v).** White powder; mp 190–192 °C. IR (KBr) (ν_{max}, cm^{-1}): 3255 (NH), 1645 (C=O). MS (m/z, %): 375 (M^+, 8). ^{1}H NMR (250 MHz, d_6-DMSO): δ 7.09 (1 H, t $J = 8$ Hz, CH), 7.47–8.34 (14 H, aromatic), 9.23 (2 H, d, $J = 8$ Hz, 2 NH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 58.6 (CH), 121.4, 122.7, 129.9, 133.5, 133.7 and 147.8 (aromatic carbons of aldehyde moiety), 127.6, 128.3, 131.7 and 142.4 (carbons of two phenyl rings), 165.9 (C=O). Analyses: Calcd. for $C_{21}H_{17}N_3O_4$: C, 67.19; H, 4.56; N, 11.19. Found: C, 67.1; H, 4.4; N, 11.3.

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