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Synthesis of N,N'-Arylidene Bisamides Using Stannic Chloride Pentahydrate as Catalyst

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An efficient one-pot synthesis of N,N'-alkylidene bisamides is accomplished by a condensation reaction of aromatic aldehydes and amines under solvent-free conditions in the presence of stannic chloride pentahydrate. This method has the advantages of mild reaction conditions, lack of special apparatus and toxic organic reagent, simple work-up, cost efficiency and environment friendly.

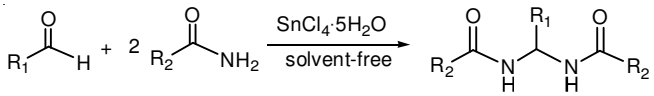
Keywords: N,N'-Alkylidene bisamides, Amides, Aldehydes, Stannic chloride pentahydrate.

INTRODUCTION

Bisamides are useful synthetic intermediates in organic synthesis, since these groups can be easily transformed into other functionalities. Specifically, bisamides are key fragments for the introduction of *gem*-diaminoalkyl residues in retro-inverse pseudopeptide derivatives[1] and are of considerable interest in the synthesis of pharmacological materials such as peptidomimetic compounds[2]. Therefore, preparation of amides has attracted considerable attention in the past and in recent years.

The common approach to prepare bisamides all applied the reaction of aldehydes with the corresponding amides using different catalysts under microwave irradiation and conventional heating, such as sulfuric acid (85 %, also as solvent)[3], triflic acid[4], sulfonic acid[5], sulfamic acid[6], *p*-toluenesulfonic acid[7], boric acid[8], phosphotungstic acid[9], silica supported polyphosphoric acid[10], molybdate sulfuric acid and silica sulfuric acid[11]. However, these methods show varying degrees of success as well as limitations such as the requirement of special apparatus, harsh reaction conditions, use of an excess of expensive catalysts or toxic organic solvents. Thus, there is a certain need for the development of an alternative route for the production of N,N'-arylidene bisamides.

Metal's chlorides are often used as catalyst in organic synthesis, Shafiee reported silica-supported barium chloride[12] and magnesium chloride[13] as catalyst to catalyze the synthesis of bisamides, but in this protocol nitriles is needed as extra organic compounds to promote this reaction, or the bisamides could not form. Obviously, this results in laborious work-up procedures. In this paper, a simple and efficient route using stannic chloride pentahydrate ($SnCl_4 \cdot 5H_2O$) as catalyst is developed (**Scheme-I**), which surpasses this limitation.



Scheme-I: Synthesis of N,N'-arylidene bisamides

EXPERIMENTAL

All reagents were of analytical grade and purchased from Sinopharm Chemical Reagent Co., Ltd. and were used without further purification.

General procedure for the synthesis of N, N'-arylidene bisamides: To a stirred mixture of the amide (11 mmol) and aldehyde (5 mmol) in a round-bottomed flask equipped with condenser at 90 °C was added $SnCl_4 \cdot 5H_2O$ (0.2 mmol) and the reaction was heated for the given time. The reaction was monitored by TLC. After completion, the reaction mixture was washed with ethyl acetate and water, respectively. The crude product was obtained by simple filtration. Further purification was followed by crystallization from diethyl ether.

All the products are known compounds. The desired pure products were characterized by spectral (IR, ^{1}H NMR) and analytical data and by comparison of their physical and spectral data with those of known compounds[3-11].

N-Acetylamino(phenyl)methyl acetamide (Table-3, entry 1): White solid, m.p.: 238-240 °C; IR (KBr, ν_{max}, cm^{-1}): 3277, 1663, 1565, 1517, 1371, 1271, 1092, 848, 695; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.86 (s, 6H, $2CH_3$), 6.50 (t, J = 7.8 Hz, 1H, CH), 7.28-7.36 (m, 5H, ArH), 8.54 (d, J = 7.8 Hz, 2H, 2NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 23.1, 57.8, 126.7, 127.9, 128.6, 141.0, 169.0. Anal. calcd for $C_{11}H_{14}N_2O_2$: C 64.06, H 6.84, N 13.58; found C 64.17, H 6.90, N 13.52.

N-Acetylamino(4-chlorophenyl)methyl acetamide (Table-3, entry 2): White solid, m.p.: 258-260 °C; IR (KBr, ν_{max}, cm^{-1}): 3272, 2926, 1671, 1540, 1348, 1266, 1068, 800, 701; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.85 (s, 6H, $2CH_3$), 6.49 (t, *J* = 7.8 Hz, 1H, CH), 7.34 (d, *J* = 8.0 Hz, 2H, ArH), 7.45 (d, *J* = 8.0 Hz, 2H, ArH), 8.56 (d, *J* = 7.8 Hz, 2H, 2NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 23.5, 57.8, 123.0, 129.4, 132.7, 140.0, 169.9; Anal. calcd for $C_{11}H_{13}N_2O_2Cl$: C 54.89, H 5.41, N 11.64; found C 54.81, H 5.48, N 11.69.

N-Acetylamino(4-methylphenyl)methyl acetamide (Table-3, entry 3): White solid, m.p.: 270-272 °C; IR (KBr, ν_{max}, cm^{-1}): 3269, 1673, 1564, 1511, 1367, 1280, 1090; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.85 (s, 6H, $2CH_3$), 2.31 (s, 3H, $ArCH_3$), (t, *J* = 7.8 Hz, 1H, CH), 7.22 (d, *J* = 8.0 Hz, 2H, ArH), 8.46 (d, *J* = 7.8 Hz, 2H, 2NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 21.2, 23.0, 57.3, 126.8, 129.0, 137.1, 138.2, 169.1; Anal. calcd for $C_{12}H_{16}N_2O_2$: C 65.45, H 7.27, N 12.72; found C 65.57, H 7.21, N 12.63.

N-Acetylamino(4-methoxylphenyl)methyl acetamide (Table-3, entry 4): White solid, m.p.: 221-273 °C; IR (KBr, ν_{max}, cm^{-1}): 3271, 3066, 1681, 1550, 1511, 1280,1177, 820, 706; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.85 (s, 6H, $2CH_3$), 3.73 (s, 3H, OCH_3), 6.45 (t, *J* = 7.8 Hz, 1H, CH), 6.90 (d, *J* = 8.0 Hz, 2H, ArH), 7.27 (d, *J* = 8.0 Hz, 2H, ArH), 8.45 (d, *J* = 7.8 Hz, 2H, 2NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 21.6, 54.0, 56.0, 113.1, 127.1, 132.2, 158.0, 167.6; Anal. calcd for $C_{12}H_{16}N_2O_3$: C 61.00, H 6.83, N 11.86; found C 61.10, H 6.89, N 11.80.

N-Acetylamino(4-nitrophenyl)methyl acetamide (Table-3, entry 5): White solid, m.p.: 269-272 °C; IR (KBr, ν_{max}, cm^{-1}): 3271, 2948, 1670, 1520, 1353, 1273, 1091, 825, 772, 619; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.89 (s, 6H, $2CH_3$), 6.58 (t, *J* = 7.8 Hz, 1H, CH), 7.60 (d, *J* = 8.2 Hz, 2H, ArH), 8.25 (d, *J* = 8.2 Hz, 2H, ArH), 8.71 (d, *J* = 7.8 Hz, 2H, 2NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 23.3, 57.5, 124.0, 128.7, 147.6, 169.5; Anal. calcd for $C_{11}H_{13}N_3O_4$: C 52.59, H 5.22, N 16.73; found C 52.65, H 5.27, N 16.81.

N-Benzoylamino(phenyl)methyl benzamide (Table-3, entry 6): White solid, m.p.: 233-235 °C; IR (KBr, ν_{max}, cm^{-1}): 3278, 1650, 1540, 1497, 1340, 1266, 1044, 877, 806, 704; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.04 (t, *J* = 7.8 Hz, 1H, CH), 7.32-7.60 (m, 11H, ArH), 7.91 (d, *J* = 7.2 Hz, 4H, ArH), 9.04 (d, *J* = 7.8 Hz, 2H, 2NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 59.3, 127.5, 128.5, 129.1, 132.5, 134.7, 140.8, 166.2; Anal. calcd for $C_{21}H_{18}N_2O_2$: C 76.34, H 5.49, N 8.48; found C 76.23, H 5.56, N 8.51.

N-Benzoylamino(4-chlorophenyl)methyl benzamide (Table-3, entry 7): White solid, m.p.: 233-236 °C; IR (KBr, ν_{max}, cm^{-1}): 3279, 1644, 1542, 1493, 1345, 1266, 1068, 800, 701. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.03 (t, *J* = 7.6 Hz, 1H, CH), 7.42-7.55 (m, 10H, ArH), 7.90 (d, *J* = 7.6 Hz, 4H, ArH), 9.07 (d, *J* = 7.8 Hz, 2H, 2NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 58.5, 127.5, 128.3, 128.4, 128.6, 131.5, 132.2, 133.4, 139.0, 165.6; Anal. calcd for $C_{21}H_{17}N_2O_2Cl$: C 69.14, H 4.66, N 7.68; found C 69.23, H 4.56, N 7.61.

N-Benzoylamino(4-methylphenyl)methyl benzamide (Table-3, entry 8): White solid, m.p.: 242-244 °C; IR (KBr, ν_{max}, cm^{-1}): 3254, 2920, 2849, 1644, 1512, 1282, 1057, 701. ^{1}H NMR (400 MHz, DMSO-δ$_6$): *d* = 2.27 (s, 3H, CH_3), 7.00 (t, 1H, *J* = 7.6 Hz, ArH), 7.17 (d, 2H, *J* = 7.8 Hz, ArH), 7.34 (d, 2H, *J* = 7.8 Hz, ArH), 7.45-7.58 (m, 6H, ArH), 7.87 (d, 4H, *J* = 8.0 Hz, ArH), 8.95 (d, 2H, *J* = 7.5 Hz, 2NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 20.5, 58.5, 126.2, 127.5, 128.2, 128.6, 131.5, 133.9, 136.9, 137.3, 165.4; Anal. calcd for $C_{22}H_{20}N_2O_2$: C 76.72, H 5.85, N 8.13; found C 76.61, H 5.79, N 8.18.

N-Benzoylamino(4-methoxyphenyl)methyl benzamide (Table-3, entry 9): White solid, m.p.: 226-228 °C; IR (KBr, ν_{max}, cm^{-1}): 3279, 2958, 1653, 1546, 1515, 1280, 1249, 1060, 810, 703; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.75 (s, 3H, CH_3), 6.96-6.99 (m, 3H, ArH and CH), 7.40-7.56 (m, 8H, ArH), 7.93 (d, *J* = 7.3 Hz, 4H, ArH), 8.96 (d, *J* = 7.4 Hz, 2H, 2NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 56.0, 59.1, 114.3, 128.1, 128.4, 129.0, 132.4, 133.2, 134.5, 159.6, 166.1. Anal. calcd for $C_{22}H_{20}N_2O_3$: C 73.32, H5.59, N 7.77; found: C 73.40, H 5.69, N 7.84.

N-Acetylamino(4-nitrophenyl)methyl acetamide (Table-3, entry 10). White solid, m.p.: 266-267 °C; IR (KBr, ν_{max}, cm^{-1}): 3268, 2941, 1670, 1609, 1518, 1351, 1275, 1084, 852, 772; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.05 (t, *J* = 7.4 Hz, 1H, CH), 7.46-7.60 (m, 6H, ArH), 7.73 (d, *J* = 8.7 Hz, 2H, ArH),7.90 (d, *J* = 7.2 Hz, 4H, ArH), 8.25 (d, *J* = 8.7 Hz, 2H, ArH), 9.23 (d, *J* = 7.5 Hz, 2H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 58.5. 123.7, 127.4, 127.9, 128.4, 131.7, 133.3, 147.8, 147.5, 165.7; Anal. calcd for $C_{21}H_{17}N_3O_4$: C 67.19, H 4.56, N 11.19; found: C 67.26, H 4.47, N 11.28.

RESULTS AND DISCUSSION

Initially, in search of an effective catalyst, various catalysts including Lewis acids and Brönsted acids were tested using the reaction of acetamide and benzaldehyde as model under solvent-free conditions. A summary of the experiment optimization is provided in Table-1. It was found that $SnCl_4{\cdot}5H_2O$ was the most efficient catalyst compared with others. In addition, heating mode (microwave irradiation and conventional heating) was examined. Microwave irradiation has been used in the synthesis of bisamides[7,8], thus we attempted to carry out the reaction in MARS Microwave Reaction System of CEM corporation at 90 °C, but opposite to some reports, it is found that microwave irradiation could not significantly promote the synthesis of N,N'-arylidene bisamides, so conventional heating was employed in following experiments. It should be noted that only a trace of desired product was obtained in the absence of catalyst.

TABLE-1
SCREENING OF CATALYST

Entry	Catalyst (mol %)	Temperature (°C)	Time	Yield (%)
1	$HClO_4$ (5)	90	3h	48.0
2	I_2 (5)	90	3h	55.5
3	$ClCH_2COOH$ (5)	90	3h	18.2
4	$ZrOCl_2{\cdot}8H_2O$ (5)	90	3h	41.2
5	$Ce(NO_3)_3{\cdot}6H_2O$ (5)	90	3h	35.3
6	$C_6H_5PO_2H_2$ (5)	90	3h	58.5
7	$SnCl_4{\cdot}5H_2O$ (5)	90	3h	68.5
8	$SnCl_4{\cdot}5H_2O$ (5)	MW/90	20 min	57.0
9	$HClO_4$ (5)	MW/90	15 min	46.1
10	$Ce(NO_3)_3{\cdot}6H_2O$ (5)	MW/90	15 min	34.2
11	$ZrOCl_2{\cdot}8H_2O$ (5)	MW/90	15 min	41.6
12	-	90	3h	trace

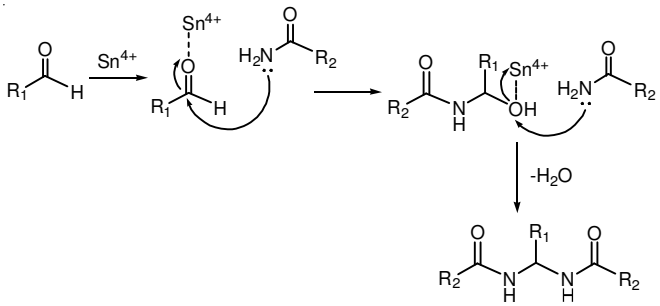
The reaction conditions were optimized using $SnCl_4·5H_2O$ as catalyst (Table-2). Firstly, to understand the effect of solvent, the reaction has been carried out with solvents-Toluene, EtOAc. A considerable amount of desired products were formed in solvents. However, best yield was still obtained under solvent-free conditions. Subsequently, the effect of the amount of catalyst was investigated in this reaction. The results showed that a 3 % mol amount of $SnCl_4·5H_2O$ was sufficient to promote the reaction and larger amounts of the catalyst did not lead to any significant changes in the reaction yield. We also tried to optimize reaction temperature. When it was carried out at 60 °C, the good yield could be obtained in a short time.

TABLE-2
OPTIMIZATION OF THE REACTION CONDITIONS FOR SYNTHESIS OF N-ACETYLAMINO(PHENYL)METHYL ACETAMIDE CATALYZED BY $SnCl_4·5H_2O$

Entry	Amount of catalyst (mol %)	Conditions (T/°C)	Time (h)	Yield (%)
1	5	Solvent-free/90	3	68.5
2	5	Toluene/90	4	50.3
3	5	EtOAc/90	4	56.0
4	3	Solvent-free/90	3	75.5
2	2	Solvent-free/90	3	70.8
3	10	Solvent-free/90	3	55.6
4	3	Solvent-free/50	3	69.8
5	3	Solvent-free/60	3	80.4
6	3	Solvent-free/70	3	77.8
7	3	Solvent-free/110	3	70.5

Using these optimized reaction conditions, the scope and efficiency of these procedures were explored for the synthesis of a wide variety of substituted bisamides. The results are summarized in Table-3. Reactions were preceded well with various aromatic aldehydes and benzamide to provide symmetrical N,N'-alkylidene bisamides. However, the reaction of benzaldehyde with formamide did not occur and only starting material was recovered in quantitative yield (Table-3, entry 11).

To explain the formation of bisamides *via* the one-pot multi-component reaction, we have proposed a plausible reaction mechanism according to the results and as in current reports[8,9], which is illustrated in **Scheme-II**.



Scheme-II: Proposed reaction mechanism for the synthesis of N,N'-arylidene bisamides catalyzed by $SnCl_4·5H_2O$

TABLE-3
SYNTHESIS OF N,N'-ARYLIDENE BISAMIDES CATALYZED BY $SnCl_4·5H_2O$

Entry	R_1	R_2	Time (h)	Yield (%)[a]
1	C_6H_5	CH_3	3	80.4
2	4-FC_6H_4	CH_3	4	85.5
3	4-$CH_3C_6H_4$	CH_3	3	77.2
4	4-$CH_3OC_6H_4$	CH_3	4	67.2
5	4-$NO_2C_6H_4$	CH_3	2.5	87.2
6	C_6H_5	C_6H_5	1.5	91.0
7	4-FC_6H_4	C_6H_5	1.0	93.0
8	4-$CH_3C_6H_4$	C_6H_5	1.5	87.3
9	4-$CH_3OC_6H_4$	C_6H_5	2.0	83.2
10	4-$NO_2C_6H_4$	C_6H_5	1.0	95.8
11	C_6H_5	H	4	-

[a]Isolated yield

Conclusion

Stannic chloride pentahydrate has been successfully used as an effective catalyst for the synthesis of symmetrical N,N'-alkylidene bisamides. It is applicable to a wide scope of structural types using low mole percent of the catalyst; moreover, this procedure offers some advantages in terms of milk reaction conditions, simple workup procedure, cost efficiency, lack of special apparatus and toxic organic reagent, so this method is practical and attractive.

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