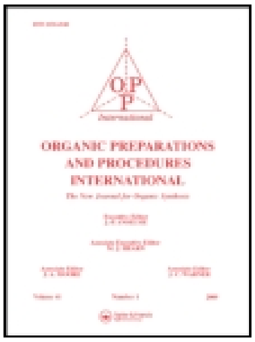

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An Efficient Synthesis of Symmetrical *N,N′*-Alkylidene *bis*-Amides Catalyzed by a Heteropolyacid

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Amides and polyamides have been found as a key component of many biologically active and pharmaceutically useful compounds. In particular, symmetrical and unsymmetrical *N,N′*-alkylidene *bis*-amides and their derivatives are key structural sub-units for the construction of peptido-mimetic frameworks.[1–2]

A literature survey revealed that, for the preparation of *bis*-amides from aldehydes and primary amides, several methods have been reported using different homogeneous or heterogeneous catalysts and catalytic systems, such as aqueous sulfuric acid,[3] trifluoromethanesulfonic acid (CF_3SO_3H),[4] sulfamic acid (NH_2SO_3H),[5] *p*-toluenesulfonic acid (*p*-TSA),[6] silica-supported barium chloride (SiO_2-$BaCl_2$),[7] boric acid [$B(OH)_3$],[8] phosphotungstic acid (PWA),[9] silica-supported perchloric acid ($HClO_4$-SiO_2),[10] silica-supported polyphosphoric acid (SiO_2-PPA),[11] silica-supported magnesium chloride (SiO_2-$MgCl_2$),[12] and *tris* (hydrogensulfato)boron [$B(HSO_4)_3$],[13] and nano-$SnCl_4.SiO_2$.[14] However, several of these methods suffer from some drawbacks such as prolonged reactions times, utilization of hazardous organic solvents, tedious work-up conditions, use of microwave irradiation,[8] employment of large amounts of catalyst. The present work reports the use of $H_{14}[NaP_5W_{29}MoO_{110}]$ as a catalyst for the preparation of symmetrical *N,N′*-alkylidene *bis*-amides (*Scheme 1*). Recently, heteropolyacids (HPAs), such as $H_{14}[NaP_5W_{29}MoO_{110}]$, $H_5[\alpha$- $SiMo_2VW_9O_{40}].xH_2O$, and $H_5[PW_{10}V_2O_{40}]$ have gained importance as environmentally friendly and economically viable solid acids because of their ready availability, high thermal stability, low cost, ease of handling, and recyclability. In comparison with liquid mineral acids, heteropolyacids (HPAs), can be separated easily from the reaction mixture by simple filtration with high recovery. These features lead to decreasing equipment cauterization and environment pollution; these catalysts exhibit high activities and unique selectivities thus allowing for cleaner reactions than conventional ones and hence may be regarded as green reagents. They also act as bifunctional catalysts under homogeneous as well as heterogeneous conditions.[15–17] HPAs are stronger than some mineral acids such as H_2SO_4, HCl, and HNO_3.[18]

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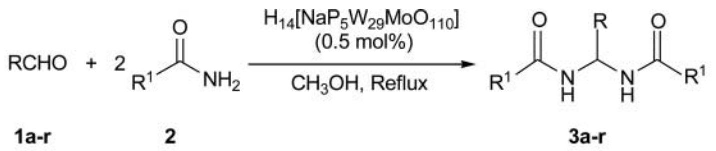
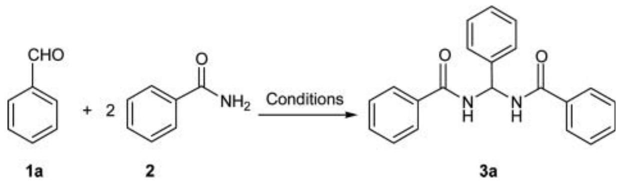


3a) R = C_6H_5, R^1 = C_6H_5. **3b)** R = 4-$NO_2C_6H_4$, R^1 = C_6H_5. **3c)** R = 4-CNC_6H_4 , R^1 = C_6H_5. **3d)** R = 3-$NO_2C_6H_4$, R^1 = C_6H_5 **3e)** R = 2-$NO_2C_6H_4$, R^1 = C_6H_5 **3f)** R = 4-ClC_6H_4, R^1 = C_6H_5 **3g)** R =2,4-ClC_6H_3, R^1 = C_6H_5 **3h)** R = 3-ClC_6H_4, R^1 = C_6H_5 **3i)** R = 4-BrC_6H_4, R^1 = C_6H_5 **3j)** R = 3 BrC_6H_4, R^1 = C_6H_5 **3k)** R = 2-MeC_6H_4, R^1 = C_6H_5 **3l)** R = 4-MeC_6H_4, R^1 = C_6H_5 **3m)** R =3-$PhOC_6H_4$, R^1 = C_6H_5 **3n)** R = H, R^1 = C_6H_5 **3o)** R = $C_6H_5CH{=}CH$, R^1 = C_6H_5, **3p)** R = 4-$NO_2C_6H_4$, R^1 = CH_3 **3q)** R = 4-BrC_6H_4 , R^1 = CH_3 **3r)** R = 3-$NO_2C_6H_4$, R^1 = CH_3

Scheme 1

The development of methodologies that involve the use of inexpensive and re-usable catalysts under mild and environmentally friendly conditions is one of the major goals in green and sustainable chemistry. Methodologies leading to various organic compounds are in high demand for both academic and industrial applications.[19–23] As a continuation

Table 1
Various Conditions Used for the Synthesis of *N,N′*-(Phenylmethylene)dibenzamide



Entry	Solvent	Temperature(°C)	Time (min)	Yield (%)
1	Ethanol	Reflux	90	80
2	Methanol	Reflux	90	86
3	Ethyl acetate	Reflux	90	46
4	Acetonitrile	Reflux	90	80
5	Toluene	Reflux	90	80
6	Dichloromethane	Reflux	90	28
7	1,4-Dioxane	Reflux	90	82
8	Solvent-free	100	90	54
9	Methanol[a)]	Reflux	90	78
10	Methanol[b)]	Reflux	90	88
11	Methanol[c)]	Reflux	90	45
12	Methanol[d)]	Reflux	90	72
13	Methanol[e)]	Reflux	180	–[f)]

a)$H_{14}[NaP_5W_{29}MoO_{110}]$ (0.08 g) used in model reaction. b)$H_{14}[NaP_5W_{29}MoO_{110}]$ (0.25 g) used in model reaction; c)$H_5[\alpha\text{-}SiMo_2VW_9O_{40}].xH_2O$ (0.15 g) used in model reaction; d)$H_5[PW_{10}V_2O_{40}]$ (0.15 g) used in model reaction; e)In the absence of any catalyst. f)No reaction.

of our work on the development of efficient and environmentally benign reagents and catalysts,[24–30] we now report that $H_{14}[NaP_5W_{29}MoO_{110}]$ is an excellent catalyst for the synthesis of symmetrical *N,N′*-alkyli-dene *bis*-amide derivatives.

In order to explore the catalytic activity of $H_{14}[NaP_5W_{29}MoO_{110}]$, prepared according to the literature procedure,[17] the condensation of benzaldehyde (1 mmol) with benzamide (2 mmol) in the presence of the catalyst (0.15 g) was initially carried out as a model reaction by heating in different solvents (1 ml) to examine its effect on the yield and rate of the reaction to give *N,N′*-(phenylmethylene)dibenzamide (**3a**) (*Table 1, Entries 1–7*). While the yield and the rate of reaction were quite good when methanol was used as solvent (*Entry 2*), only a 54% yield of the product was obtained under solvent-free conditions, at 100°C and after 100 min (*Entry 8*). To optimize the amount of catalyst required, the reaction was performed using various catalyst loadings (*Entries 9 and 10*).

In comparison with $H_{14}[NaP_5W_{29}MoO_{110}]$, the use of $H_5[\alpha\text{-}SiMo_2VW_9O_{40}].xH_2O$ and of $H_5[PW_{10}V_2O_{40}]$ as catalysts afforded lower yields in the model reaction under the same condi-tions (*Entries 11 and 12*); in the absence of catalyst, the reaction did not proceed at all even upon prolonged reaction times (*Entry 13*). This success led us to apply these conditions to the condensation of a wide variety of aromatic aldehydes containing both electron-withdrawing and electron-donating groups and of aliphatic aldehydes. The corresponding symmetrical *N,N′*-alkylidene *bis*-amides were obtained; aromatic aldehydes bearing electron-withdrawing groups reacted more rapidly than those with electron-donating substituents. The reaction of formaldehyde (***3n***) and cinnamaldehyde (***3o***) proceeded more slowly and gave lower yields while 4-nitroacetophenone and

Table 2

Synthesis of Symmetrical *N,N′*-Alkylidene *bis*-Amide Derivatives

					mp (°C)	
Products (**3a–r**)	R	R^1	Yield (%)	Time (min)	Found	Lit.
3a	C_6H_5	C_6H_5	86	90	217–219	214–216[14]
3b	$4\text{-}NO_2C_6H_4$	C_6H_5	94	50	255–257	259–261[13]
3c	$4\text{-}CNC_6H_4$	C_6H_5	95	50	234–236	230–234[8]
3d	$3\text{-}NO_2C_6H_4$	C_6H_5	92	60	226–228	232–235[13]
3e	$2\text{-}NO_2C_6H_4$	C_6H_5	83	80	259–261	257–259[12]
3f	$4\text{-}ClC_6H_4$	C_6H_5	82	70	252–254	251–254[12]
3g	$2,4\text{-}ClC_6H_3$	C_6H_5	79	80	199–200	195–197[13]
3h	$3\text{-}ClC_6H_4$	C_6H_5	80	90	221–222	–
3i	$4\text{-}BrC_6H_4$	C_6H_5	90	70	256–258	252–254[13]
3j	$3\text{-}BrC_6H_4$	C_6H_5	82	90	226–228	–
3k	$2\text{-}MeC_6H_4$	C_6H_5	74	120	223–225	–
3l	$4\text{-}MeC_6H_4$	C_6H_5	77	100	244–246	242–243[13]
3m	$3\text{-}PhOC_6H_4$	C_6H_5	87	60	194–196	–
3n	H	C_6H_5	72	100	219–220	216–218[10]
3o	$C_6H_5CH{=}CH$	C_6H_5	42	150	198-200	199–201[14]
3p	$4\text{-}NO_2C_6H_4$	CH_3	90	60	272–274	270–272[10]
3q	$4\text{-}BrC_6H_4$	CH_3	80	90	245–247	244–246[10]
3r	$3\text{-}NO_2C_6H_4$	CH_3	82	70	232–234	231–233[6]

crotonaldehyde failed to react with benzamide under the same conditions even after 200 min, only starting material being recovered.

In order to illustrate the efficiency of our procedure, results for the preparation of *N, N′*-alkylidene *bis*-amides previously reported are compared with our data (*Table 3*). The present method using $H_{14}[NaP_5W_{29}MoO_{110}]$ as catalyst offers several advantages such as excellent yields, a simple procedure, short reaction times, facile work-up and greener conditions. The green aspect of HPA catalysts has been discussed in terms of being non-corrosive, presenting fewer disposals problem, facile isolation of the products, and recyclability.

The recycling of $H_{14}[NaP_5W_{29}MoO_{110}]$ was investigated using the synthesis of **3a**. After completion of the reaction, the solid product was collected and the filtrate was evaporated under reduced pressure to give the catalyst which was washed with diethyl ether and dried at 80°C for 2 h. It was re-used directly in the model reaction to give **3a** in yields of 86%, 80%, 72% for three consecutive runs (*Table 4*).

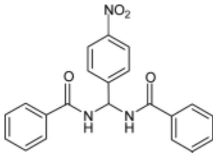
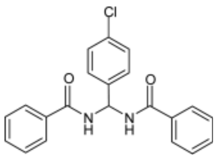
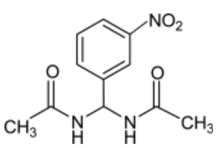
In conclusion, we have developed an alternative and simple protocol for the synthesis of symmetrical *N,N′*-alkylidene *bis*-amides using $H_{14}[NaP_5W_{29}MoO_{110}]$. These catalysts based on HPAs have several advantages over acid catalysts; they are not corrosive, are environmetally benign, present fewer disposal problems, are removed easily and are thermally stable.

Experimental Section

All reagents were obtained from commercial sources and were used without purification. IR spectra were recorded as KBr pellets on a Shimadzu 435-U-04 spectrophotometer. ^1H and ^{13}C NMR spectra were determined on a Bruker DRX-300 Avance spectrometer in

Table 3

Comparison of the Efficiencies of Various Catalysts used in the Synthesis of *N,N′*-Alkylidene *bis*-Amides

Entry	*N,N′*-Alkylidene *bis*-Amides	Conditions	Time (min)	Yield (%)
3b		SiO_2-$BaCl_2$/ 100°C/solvent-free[7]	90	91
		$B(OH)_3$/toluene/reflux[8]	1800	65
		PWA//toluene/reflux[9]	1200	71
		Present work	50	94
3f		$B(OH)_3$/toluene/reflux[8]	2880	65
		SiO_2-$MgCl_2$/ 100°C/solvent-free[12]	120	74
		Present work	70	82
3r		Sulfamic acid/ 125°C/Solvent-Free[5]	1080	68
		Present work	70	82

DMSO-d_6 or $CDCl_3$, and shifts are given in δ downfield from tetramethylsilane (TMS) as an internal standard. Melting points were determined using an Electrothermal 9200 apparatus and are uncorrected.

General Procedure for the Synthesis of Symmetrical *N,N′*-Alkylidene *bis*-Amides

The catalyst, $H_{14}[NaP_5W_{29}MoO_{110}]$ (0.5 mol%, 0.15 g), was added to a mixture of the aldehyde (1 mmol), the amide (2 mmol), and 1 mL of methanol in a 5 mL flask fitted with a reflux condenser. The resulting mixture was heated to reflux (an oil bath) for the appropriate time (*see Table 2*) with stirring (spin bar). After the completion of the reaction as determined by TLC (hexane-ethyl acetate, 4:1), the mixture was cooled to room temperature. The solid product which separated, was collected and recrystallized from ethanol (96%, 3 ml) to afford the pure symmetrical *N,N′*-alkylidene *bis*-amide (**3a–r**).

Analytical Data for New Compounds

***N,N′*-(3-Chlorophenylmethylene)dibenzamide (3h)**: IR: 3280, 1675, 1540, 1510, 1480, 1330, 1280, 1080, 715, 690;^{1}H NMR (300 MHz, DMSO-d_6): δ 7.04 (t, 1H, CH), 7.14–7.31 (m, 6H), 7.61–7.72 (m, 5H), 7.81 (d, 2H), 7.92 (s, 1H), 8.00 (d, 2H, NH, D_2O exchangeable); ^{13}C NMR (75 MHz, DMSO-d_6): δ 59.12, 124.14, 127.5, 128.08, 128.72, 128.81, 129.01, 132.04, 134.32, 137.85, 140.70, 165.61.

Anal. Calcd for $C_{21}H_{17}ClN_2O_2$: C, 69.14; H, 4.70; N, 7.68. Found: C, 69.19; H, 4.81; N, 7.72.

***N,N′*-(3-Bromophenylmethylene)dibenzamide (3j)**: IR: 3280, 1675, 1540, 1510, 1480, 1330, 1280, 1080, 715, 690;^{1}H NMR (300 MHz, DMSO-d_6): δ 6.94 (t, 1H, CH), 7.31–7.42 (m, 6H), 7.51–7.60 (m, 5H), 8.09 (d, 2H), 7.82 (s, 1H), 7.94 (d, 2H, NH, D_2O exchangeable); ^{13}C NMR (75 MHz, DMSO-d_6): δ 59.31, 114.70, 127.65, 128.08, 128.71, 128.91, 129.91, 132.31, 133.72, 134.91, 159.31, 166.61.

Anal. Calcd for $C_{21}H_{17}BrN_2O_2$: C, 61.63; H, 4.18; N, 6.85. Found: C, 61.70; H, 4.23; N, 6.89.

***N,N′*-(2-Methylphenylmethylene)dibenzamide (3k)**: IR: 3290, 1660, 1560, 1510, 1480, 1400, 1150, 720;^{1}H NMR (300 MHz, DMSO-d_6): δ 2.82 (s, 3H, CH_3), 6.92 (t, 1H, CH), 7.16–7.22 (m, 2H), 7.44–7.56 (m, 8H), 7.91 (d, 4H), 8.80 (d, 2H, NH, D_2O exchangeable); ^{13}C NMR (75 MHz, DMSO-d_6): δ 58.41, 117.01, 117.61, 128.41, 129.24, 129.61, 129.92, 132.41, 134.68, 137.79, 164.51, 167.70.

Anal. Calcd for $C_{22}H_{20}N_2O_2$: C, 76.73; H, 5.85; N, 8.14. Found: C, 76.77; H, 5.87; N, 8.19.

Table 4
Reusability of the $H_{14}[NaP_5W_{29}MoO_{110}]$ for the Synthesis of *N,N′*-(phenylmethylene)-dibenzamide (**3a**) after 90 min.

Entry	Number of Recycle	Yield (%)
1	1	86
2	2	80
3	3	72

N,N′-(3-Phenoxyphenylmethylene)dibenzamide (3m): IR: 3310, 1705, 1580, 1540, 1480, 1340, 1210, 710;^{1}H NMR (300 MHz, DMSO-d_6): δ 6.91 (t, 1H, CH), 6.97–7.14 (m, 5H), 7.22–7.24 (d, 2H), 7.33–7.57 (m, 9H), 7.86–7.98 (d, 4H), 9.00 (d, 2H, NH, D_2O exchangeable); ^{13}C NMR (75 MHz, DMSO-d_6): δ δ 58.46, 116.49, 117.50, 118.71, 121.58, 123.54, 127.46, 128.28, 129.93, 129.99, 131.56, 133.73, 133.77, 142.53, 156.29, 156.70, 165.59, 165.67.

Anal. Calcd for $C_{27}H_{22}N_2O_3$: C, 76.76; H, 5.25; N, 6.63. Found: C, 76.79; H, 5.28; N, 6.67.

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