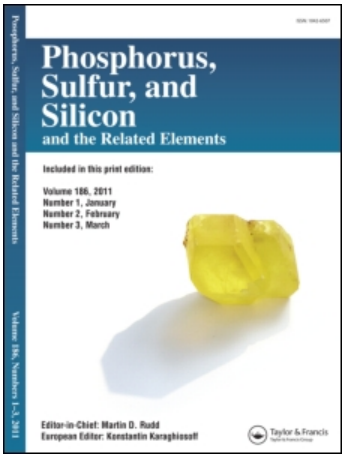

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TETRABUTYLAMMONIUM HYDROGEN SULFATE: AN EFFICIENT CATALYST FOR THE SYNTHESIS OF 3,4-DIHYDROPYRIMIDIN-2(1*H*)-ONES UNDER SOLVENT-FREE CONDITIONS

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*Tetrabutylammonium hydrogen sulfate (TBAHS) as a solid protic acid and phase-transfer reagent catalyzed the three-component condensation reactions of aldehydes, 1,3-dicarbonyl compounds, and urea or thiourea under solvent-free conditions leading to 3,4-dihydropyrimidin-2(1*H*)-ones in high yields at 80°C.*

Keywords: Biginelli reaction; condensation reaction; dihydropyrimidinones; solvent free; tetrabutylammonium hydrogen sulfate

INTRODUCTION

Dihydropyrimidinones (DHPMs) and their derivatives are pharmacologically important compounds as calcium channel blockers, antihypertensive agents, α-1-a-antagonists, and neuropeptide Y(NPY) antagonists.[1] In addition, the dihydropyrimidinone-5-carboxylate core unit is found in many marine natural products, including the batzelladine alkaloids, which have been found to be potent HIVgp-120-CD_4 inhibitors.[2] Therefore, many synthetic methods for preparing such compounds under classical reflux[3–8] or solvent-free conditions[9–15] and microwave[16–19] or ultrasonic irradiation[20,21] have been reported.

Very recently, we and Reddy groups reported ammonium chloride[13] and *N*-butyl-*N*,*N*-dimethyl-α-phenylethyl ammonium bromide[15] as efficient reagents for accelerating Biginelli reaction under solvent-free

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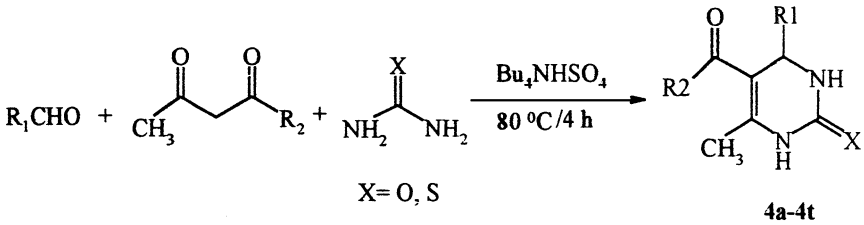
conditions. Product yields were good, but both of these methods carried at relatively high temperature, at 100°C. In addition, although NH_4Cl is a very cheap reagent, *N*-butyl-*N*,*N*-dimethyl-α-phenylethyl ammonium bromide is relatively expensive. Therefore, the introduction of an alternative and an inexpensive new phase transfer reagent for the accelerating of Biginelli reaction under solvent-free conditions and lower temperature is of prime importance.

In continuation of our previous work on solvent-free organic transformations[22–24] and using tetrabutylammonium hydrogen sulfate as catalyst,[25] we wish to report the results obtained from a study of the preparation of 3,4-dihydropyrimidin-2(1*H*)-ones using tetrabutylammonium hydrogen sulfate under solvent-free conditions at 80°C (Scheme 1).



SCHEME 1

RESULTS AND DISCUSSION

Tetrabutylammonium hydrogen sulfate with dual properties as solid protic acid and phase-transfer reagent efficiently catalyzed the Biginelli reaction under solvent-free conditions at 80°C. Table I summarizes the results for the application of this procedure to a series of reactants. The procedure gives products in good yields and avoids problems connected with solvent use (cost, handling, safety, and pollution). Decreased reaction times are also realized because of increased reactivity of the reactants in the solid state and the fact that water, as a reaction product, is evaporated at the reaction temperature at 80°C. Even for aliphatic aldehydes which normally show extremely poor yields in the Biginelli reaction,[17] 68 and 59% yields of the corresponding dihydropyrimidin-2(1*H*)-ones **4f** and **4g** could be obtained. Importantly, aromatic aldehydes carrying either electron-donating (—OMe) or electron-withdrawing ($-NO_2$) substituents all reacted very well, giving moderate-to-excellent yields of the desired products using this catalyst.

In order to improve the yield, we have tested various amounts of tetrabutylammonium hydrogen sulfate with a model reaction

TABLE I Tetrabutylammonium Hydrogen Sulfate Catalyzed Syntheses of 3,4-dihydropyrimidin-2(1*H*)-ones under Solvent-Free Conditions at 80°C

					m.p. (°C)	
DHMP	R_1	R_2	X	Yield (%)[a]	Found	Reported
4a	C_6H_5	OEt	O	90	202–203	201–203[b]
4b	4-$MeOC_6H_4$	OEt	O	88	200–201	199–201[b]
4c	4-ClC_6H_4	OEt	O	85	209–211	210–212[b]
4d	4-$O_2NC_6H_4$	OEt	O	85	206–208	207–210[b]
4e	3-$O_2NC_6H_4$	OEt	O	77	224–226	226–228[c]
4f	C_3H_7	OEt	O	68	153–154	153–155[d]
4g	C_4H_9	OEt	O	59	154–156	157–158[b]
4h	C_6H_5	OMe	O	93	210–211	207–210[b]
4i	4-$O_2NC_6H_4$	OMe	O	78	235–236	235–237[b]
4j	4-$MeOC_6H_4$	OMe	O	91	193–194	191–193[b]
4k	4-ClC_6H_4	OMe	O	75	206–208	204–207[e]
4l	3-$O_2NC_6H_4$	OMe	O	88	280–282	—
4m	C_6H_5	Me	O	73	231–232	233–236[b]
4n	4-$MeOC_6H_4$	Me	O	87	180–181	178–180[b]
4o	4-$O_2NC_6H_4$	Me	O	83	228 (dec)	230 (dec)[b]
4p	C_6H_5	OEt	S	87	204–205	205–207[c]
4q	4-$MeOC_6H_4$	OEt	S	85	138–139	140[f]
4r	3-$O_2NC_6H_4$	OEt	S	81	203–205	206–207[c]
4s	C_6H_5	OBn	O	91	166–168	—
4t	4-$MeOC_6H_4$	OBn	O	92	187–188	—

[a]Isolated yield.
[b]Reddy et al.[5]
[c]Shaabani et al.[13]
[d]Eynde et al.[26]
[e]Peng and Deng.[14]
[f]Singh et al.[27]

using benzadehyde (1 mmol), ethyl acetoacetate (1 mmol), and urea (1.5 mmol) at different temperatures. As shown in Table II, increasing the quantity of the catalyst can improved the reaction yields at each temperature. The best results were obtained by carrying out the reaction at 80°C in the presence of 0.30 mmol of catalyst. Higher amount of catalyst or temperature did not improve the yield to a greater extent.

Also we scaled up the reaction to the level producing multigrams of product using electron-donating (—OMe) or electron-withdrawing ($—NO_2$) substituents without any problems (see the Experimental section below).

In summary, with the use of tetrabutylammonium hydrogen sulfate as an inexpensive and available catalyst under solvent-free reaction conditions, the yields of the Biginelli reaction are identical to those obtained under NH_4Cl and *N*-butyl-*N*,*N*-dimethyl-α-phenylethyl

TABLE II Condensation of Benzaldehyde, Ethyl Acetoacetate, and Urea under Different Conditions

Amount of catalyst (mmol)	Yield (%)[a]			
	At 70°C	At 80°C	At 90°C	At 100°C
0	35	51	62	68
0.15	46	79	80	81
0.2	50	85	85	86
0.3	54	90	88	90
0.4	61	90	90	92

[a]Benzaldehyde (1 mmol), ethyl acetoacetate (1 mmol), urea (1.5 mmol), reaction time 4 h at 80°C.

ammonium bromide; however, the reaction temperature decreased from 100°C to 80°C. Due to its good reactivity and reduced hazardous pollution, this reagent can be recommended as a practical catalyst for aliphatic and aromatic aldehydes carrying either electron-releasing or electron-withdrawing substitution with β-ketoester as well as β-diketo compounds under solvent-free conditions.

EXPERIMENTAL

Melting points were measured on an Electrothermal 9100 apparatus and are uncorrected. 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 a BRUKER DRX-500 AVANCE spectrometer at 500.13 and 125.77 MHz, respectively. NMR spectra were obtained on solutions in DMSO-d_6. The chemicals used in this work were purchased from Fluka chemical company (Buchs, Switzerland). All the products (except **4l**, **4s**, and **4t**) are known compounds and were characterized by IR and ^{1}H NMR spectroscopic data, and their melting points were compared with reported literature values.

Tetrabutylammonium Hydrogen Sulfate Catalyzed Synthesis of 5-Ethoxycarbonyl-6-methyl-4-(4-nitrophenyl)-3,4-dihydropyrimidin-2(1*H*)-one under Solvent-Free Conditions (4d)

Small Scale

A mixture of 4-nitrobenzaldehyde (0.15 g, 1 mmol), ethyl acetoacetate (0.13 g, 1 mmol), urea (0.09 g, 1.5 mmol), and Bu_4NHSO_4 (0.10 g,

0.30 mmol) were finely mixed together. The reaction mixture in a screw-capped vial containing a magnetic stirring bar was heated at 80°C in a preheated oil batch for 4 h. After cooling, the reaction mixture was poured onto crushed ice (40 g) and stirred for 5–10 min. The solid separated was filtered under suction, washed with cold water (40 ml) and then recrystallized from ethyl acetate:*n*-hexane (1:3) to afford the pure product **4d** (0.26 g, 85%). Mp 206–208°C; IR (KBr) ($\nu_{max,}$ cm^{-1}): 3215, 1731, 1707, 1641; ^{1}H NMR (DMSO-d_6):δ_H 1.07 (3H, t, $^3J = 6.8$ Hz, CH_3), 2.26 (3H, s, CH_3), 3.97 (2H, q, $^3J = 5.4$ Hz, OCH_2), 5.27 (1H, s, CH), 7.50 (2H, d, $^3J = 7.3$ Hz, arom), 7.87 (1H, s, NH), 8.20 (2H, d, $^3J = 7.2$ Hz, arom), 9.33 (1H, s, NH); ^{13}C NMR: δ_C 14.5, 18.3, 54.2, 59.8, 98.7, 124.2, 128.1, 147.2, 149.8, 152.2, 152.5, 165.5; MS (*m/z*, %) 305 (M^+, 25), 276 (92), 260 (20), 183 (100).

It is important to note that we have to close the cap of the vial for low boiling aldehydes (**4f**, **4g**).

Large Scale

(1) 4-Nitrobenzaldehyde (1.50 g, 10 mmol), ethyl acetoacetate (1.30 g, 10 mmol), urea (0.90 g, 15 mmol), and Bu_4NHSO_4 (1.0 g, 3 mmol) were finely mixed together. The reaction mixture was heated at 80°C in a preheated oil batch for 4 h in a 25 ml round-bottomed flask containing a magnetic stirring bar. After cooling, the reaction mixture was poured onto crushed ice and stirred for 5–10 min. The solid separated was filtered under suction, washed with cold water, and then recrystallized from ethyl acetate:*n*-hexane (1:3) to afford the pure product **4d** (2.50 g, 8.2 mmol, 82%).

(2) Anisaldehyde (1.36 g, 10 mmol), ethyl acetoacetate (1.30 g, 10 mmol), urea (0.90 g, 15 mmol), and Bu_4NHSO_4 (1.0 g, 3 mmol) were finely mixed together. The reaction mixture was heated at 80°C in a preheated oil batch for 4 h in a 25 ml round-bottomed flask containing a magnetic stirring bar. After cooling, the reaction mixture was poured onto crushed ice and stirred for 5–10 min. The solid separated was filtered under suction, washed with cold water, and then recrystallized from ethyl acetate:*n*-hexane (1:3) to afford the pure product **4b** (2.31 g, 8.4 mmol, 84%).

5-Methoxycarbonyl-6-methyl-4-(3-nitrophenyl)-3,4-dihydropyrimidin-2(1*H*)-one (4l)

m.p. 280–282°C. IR (KBr) ($\nu_{max,}$ cm^{-1}): 3340, 3200, 3088, 1690, 1631. ^{1}H NMR (DMSO-d_6): δ_H 2.27 (3H, s, CH_3), 3.53 (3H, s, OCH_3), 5.29 (1H, s, CH), 7.61–8.12 (4H, m, arom), 7.90 (1H, s, NH), 9.37 (1H, s, NH). ^{13}C

NMR: δ_C δ 18.4, 51.4, 53.8, 98.6, 121.4, 122.8, 130.7, 133.4, 147.2, 148.3, 150.1, 152.3, 166.1. MS (*m/z*, %) 292 ($M^+ + H$, 25), 232 (92),169 (100).

5-Benzyloxycarbonyl-6-methyl-4-(phenyl)-3,4-dihydropyrimidin-2(1*H*)-one (4s)

m.p. 166–168°C. IR (KBr) ($\nu_{max,}$ cm^{-1}): 3345, 3218, 3100, 1703, 1637. ^1H NMR (DMSO-d_6): δ_H 2.26 (3H, s, CH_3), 5.00 and 5.04 (2H, AB-system, $^3J = 12.7$ Hz, OCH_2), 5.16 (1H, d, $^3J = 2.9$ Hz, CH), 7.13–7.30 (9H, m, arom), 7.72 (1H, s, NH), 9.23 (1H, s, NH). ^{13}C NMR: δ_C 18.3, 54.4, 65.3, 99.2, 126.7, 127.8, 128.0, 128.2, 128.7, 128.9, 137.0, 145.1, 149.7, 152.4, 165.5; MS (*m/z*, %) 322 (M^+, 45), 231 (19), 187 (20), 77 (100).

5-Benzyloxycarbonyl-6-methyl-4-(4-methoxyphenyl)-3,4-dihydropyrimidin-2(1*H*)-one (4t)

m.p. 187–188°C; IR (KBr) ($\nu_{max,}$ cm^{-1}): 3340, 3210, 3100, 1695, 1630, 1603; ^1H NMR (DMSO-d_6): δ_H 2.25 (3H, s, CH_3), 3.71 (3H, s, OCH_3), 4.99 and 5.04 (2H, AB system, $^3J = 12.7$ Hz, OCH_2), 5.12 (1H, s, CH), 6.83–7.27 (9H, m, arom), 7.68 (1H, s, NH). 9.21 (1H, s, NH). ^{13}C NMR: δ_C 18.3, 53.8, 55.5, 65.2, 99.5, 114.2, 127.9, 128.0, 128.2, 128.7, 137.0, 137.3, 149.4, 152.4, 159.0, 165.6. MS (*m/z*, %) 351 (M^+, 37), 321 (59), 216 (20), 77 (100).

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