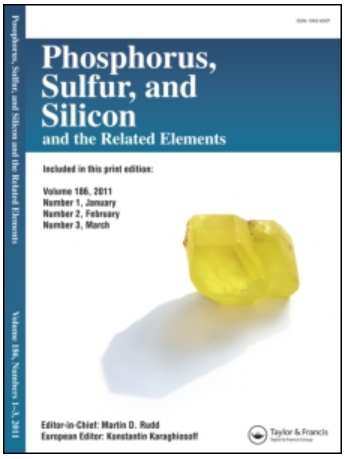

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A Simple and Efficient One-Step Synthesis of 2,4,10a-Triaryl-1,10a-Dihydro-2*H*-Pyrazino[2,1-*b*][1,3] Benzothiazoles Catalyzed by *p*-Toluene Sulfonic Acid

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A Simple and Efficient One-Step Synthesis of 2,4,10a-Triaryl-1,10a-Dihydro-2*H*-Pyrazino[2,1-*b*][1,3] Benzothiazoles Catalyzed by *p*-Toluene Sulfonic Acid

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A series of 2,4,10a-triaryl-1,10a-dihydro-2H-pyrazino[2,1-b][1,3]benzothiazoles were prepared in good yields by the reaction of 2-[(2-oxo-2-arylethyl) anilino]-1-aryl-1-ethanones with 2-aminothiophenol in the presence of p-toluenesulfonic acid under solventless conditions. The products were characterized by ^{1}H NMR and ^{13}C NMR spectroscopy.

Keywords Benzothiazole; pyrazine; *p*-toluenesulfonic acid; microwave irradiation

INTRODUCTION

Benzothiazole and pyrazine units assume importance, as they are found in many biologically active compounds. Pyrazines are found in the luminescent chromophores of certain marine organisms[1]; in cephalostatins isolated from Cephalodiscus Gilehrist, which are powerful anticancer agents;[2] in the fungal metabolite aspergillic acid;[3] and in foods as potent flavor compounds.[4] Moreover, several fungal metabolites such as glyantripine,[5] fumiquinazolines F and G,[6,7] fiscalin B,[8,9] and N-acetylardeemin,[10,11] and some spiro compounds such as fumiquinazoline C,[6,7] spiroquinazoline,[12] and alantrypinone[13] contain a pyrazino[2,1-b]moiety. Heterocycles containing a thiazole

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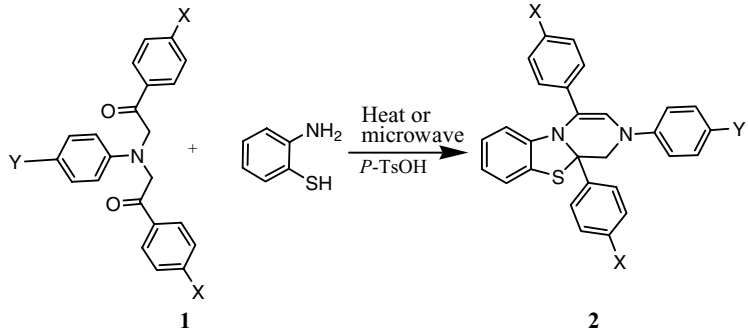


1 **2**

SCHEME 1

moiety are present in many natural products such as bleomycin,[14] epothilone A,[15] lyngbyabellin A[16] and dolastatin 10.[17] Benzothiazole derivatives have been shown to possess antimicrobial properties[18] and have found applications in industry as antioxidants[19] and vulcanization accelerators.[20] The previously discussed bioapplications of these two classes of heterocycles prompted us to synthesize 2,4,10a-triaryl-1,10a-dihydro-2*H*-pyrazino[2,1-*b*][1,3]benzothiazoles (Scheme 1) comprising of both pyrazine and benzothiazole rings under solventless conditions, and the results are presented in this article. The development of simple, efficient, and environmentally benign chemical processes or methodologies to obtain organic compounds from readily available reagents is one of the major challenges for chemists in organic synthesis, and a solventless reaction to offer target molecules is one such process.

RESULTS AND DISCUSSION

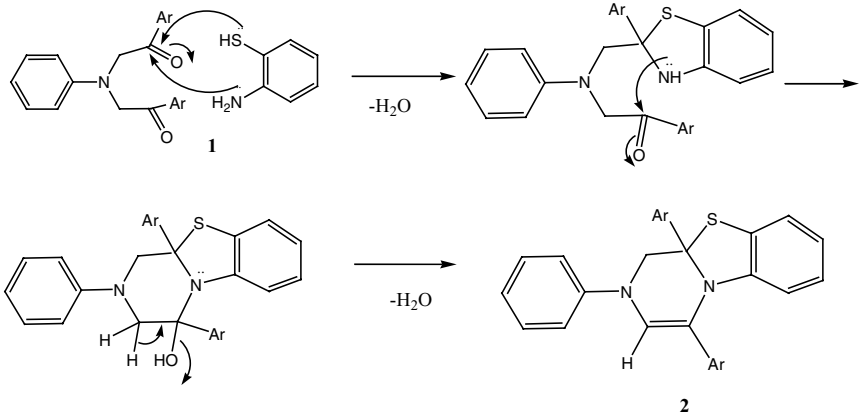
A simple protocol has been developed that allowed the crucial dialkylation of anilines with phenacyl bromides to give diphenacyl anilines **1** efficiently under solvent-free conditions. It was found that by simple mixing of phenacylbromide, aniline, and potassium carbonate in a ratio 2:1:1 and by leaving the mixture for 3 h at r.t., compound **1** was obtained in good yields with adequate purities for the next stage.[21] This solvent-free synthetic method assumes considerable interest because of the economical and environmental concerns associated with organic solvents. Slurry obtained by the addition of 1.5 mmol of 2-[(2-oxo-2-arylethyl) anilino]-1-aryl-1-ethanone **1** with 1.5 mmol of 2-aminothiophenol and a catalytic amount of *p*-toluenesulfonic acid were heated over a water bath for 15–20 min. The progress of the reaction was monitored by TLC, and the product formed in relatively good yield was found to be 2,4, 10a-triaryl-1,10a-dihydro-2*H*-pyrazino[2,1-*b*][1,3]benzothiazole **2**. The

TABLE I Physical Data of 2,4,10a-Triaryl-1, 10a-dihydro-2*H*-pyrazino[2,1-*b*] [1,3] benzothiazoles 2

			Thermal		Microwave		
Entry	X	Y	Time (min)	Yield (%)	Time (min)	Yield (%)	M.Pt. (°C)
2a	H	H	20	80	8	86	194
2b	Cl	H	16	81	7	89	238
2c	Me	H	19	82	5	86	232
2d	H	Me	19	79	8	85	189
2e	Cl	Me	15	80	6	86	225
2f	Me	Me	16	81	5	89	222

reaction of 2-aminothiophenol with a differently substituted **1** thus led to several hitherto unreported 2,4,10a-triaryl-1,10a-dihydro-2*H*-pyrazino[2,1-*b*][1,3]benzothiazoles **2** as a single product in good yield, as summarized in Table I (Scheme 1). There was no significant difference in reaction time or yield with different substituents in the tertiary amines employed. Microwave irradiation of the original reaction mixture was found to improve the yield with reduced reaction time (Table I).

The proton and carbon NMR data of the fused benzothiazoles **2** are in consonance with the structure of the products. Compound **2b** exhibited doublets at 4.04 and 4.40 ppm each with a coupling constant of 12 Hz corresponding to the diastereotopic methylenic protons. The upfield multiplet around 6.2 ppm can be assigned to the *peri* hydrogen *ortho* to the nitrogen in the benzothiazole unit. The mechanism of the



SCHEME 2

formation of the product is formulated in Scheme 2, and a similar addition of 1,5-diketone to 1,2-diamine leading to a fused heterocycle of type **2** has already been reported.[22]

CONCLUSION

This article thus describes an ecofriendly, simple, and efficient methodology for the synthesis of 2,4,10a-triaryl-1,10a-dihydro-2*H*-pyrazino[2,1-*b*][1,3]benzothiazoles, which have two biologically important heterocycles fused together.

EXPERIMENTAL

All chemicals were of reagent grade and were used without further purification. Melting points were measured on a melting point apparatus and are uncorrected. NMR spectra were recorded on a Bruker 300 MHz (Ultrashield) spectrometer. Chemical shifts are reported in ppm relative to tetramethylsilane as an internal standard. The reactions were routinely monitored by TLC on silica-gel plates. A domestic microwave oven (LG) was used for irradiation, and the reactions were carried out in 520 Watts of power.

General Procedure for the Preparation of 2,4,10a-Triaryl-1,10a-dihydro-2*H*-pyrazino[2,1-*b*][1,3]benzothiazole

A mixture of 2-[(2-oxo-2-arylethyl)anilino]-1-aryl-1-ethanone **1** (0.50 g, 1.5 mmol), 2-aminothiophenol (0.20 g, 1.5 mmol), and a catalytic amount of *p*-toluenesulfonic acid was heated on a water bath for about 15–20 min. The reaction mixture was treated with water and then extracted with dichloromethane. The organic layer was washed with water repeatedly, dried over anhydrous calcium chloride, and evaporated to give the crude product. Purification of the product was performed by column chromatography on silica gel using a petroleum ether-ethyl acetate [97:3(v/v)] mixture as an eluent.

Irradiation of the previously discussed reaction mixture in a microwave (600 W) reduced the reaction time to 5 min with an improved yield up to 85%.

2,4,10a-Triphenyl-1,10a-dihydro-2H-pyrazino[2,1-b][1,3]-benzothiazole (2a)

Colorless solid from ethanol. ^{1}H ($CDCl_3$): 4.05 (d, 1H), 4.46 (d, 1H), 6.25 (m, 1H), 6.71 (s, 1H), 6.78–6.85 (m, 4H), 6.93–7.0 (m, 1H), 7.06–7.1 (m, 1H), 7.19–7.25 (m, 6H), 7.32–7.40 (m, 2H), 7.52–7.61 (m, 4H).

^{13}C ($CDCl_3$): 52.3, 76.2, 114.1, 117.4, 118.0, 119.7, 121.4, 122.2, 122.4, 124.2, 124.4, 126.1, 126.3, 127.1, 128.5, 128.6, 129.3, 129.8, 132.1, 137.4, 139.0, 146.1, 147.2; Anal. calcd. for $C_{28}H_{22}N_2S$: C, 80.35; H, 5.30; N, 6.69; found: C, 80.31; H, 5.31; N, 6.65.

4,10a-Bis(4-chlorophenyl)-2-phenyl-1,10a-dihydro-2H-pyrazino[2,1-b][1,3]benzothiazole (2b)

Pale yellow solid from ethanol. ^1H ($CDCl_3$): 4.04 (d, 1H), 4.40 (d, 1H), 6.22 (m, 1H), 6.68 (s, 1H), 6.80–6.88 (m, 4H), 7.0–7.10 (m, 2H), 7.18–7.22 (m, 2H), 7.28–7.35 (m, 4H), 7.45–7.54 (m, 4H).^{13}C ($CDCl_3$): 52.1, 75.6, 114.1, 116.6, 117.5, 120.1, 121.8, 122.6, 122.7, 124.2, 125.1, 126.3, 128.5, 129.0, 129.5, 130.0, 131.7, 134.5, 135.6, 137.4, 145.7, 146.7. Anal. calcd. for $C_{28}H_{20}Cl_2N_2S$: C, 68.99; H, 4.14; N, 5.75; found: C, 69.01; H, 4.16; N, 5.72.

4,10a-Bis(4-methylphenyl)-2-phenyl-1,10a-dihydro-2H-pyrazino[2,1- b][1,3]benzothiazole (2c)

White solid from ethanol. ^1H ($CDCl_3$): 2.24 (s, 3H), 2.36 (s, 3H), 4.0 (d, 1H), 4.41 (d, 1H), 6.24–6.26 (m, 1H), 6.67 (s, 1H), 6.73–6.86 (m, 4H), 6.91–7.1 (m, 5H), 7.12–7.18 (m, 2H), 7.23–7.30 (m, 1H), 7.40–7.50 (m, 4H). ^{13}C ($CDCl_3$): 21.4, 21.5, 52.1, 76.2, 113.9, 117.1, 118.0, 119.0, 121.2, 122.0, 122.3, 124.1, 124.4, 126.1, 127.0, 129.3, 129.8, 130.0, 134.5, 136.0, 138.3, 146.0, 147.3. Anal. calcd. for $C_{30}H_{26}N_2S$: C, 80.68; H, 5.87; N, 6.27; found: C, 80.66; H, 5.86; N, 6.25.

2-(4-methylphenyl)-4,10a-diphenyl-1,10a-dihydro-2H-pyrazino[2,1-b][1,3]benzothiazole (2d)

White solid from ethanol. ^1H ($CDCl_3$): 2.27 (s, 3H), 4.05 (d, 1H), 4.41 (d, 1H), 6.22–6.28 (m, 1H), 6.67 (s, 1H), 6.72–6.82 (m, 2H), 7.01–7.1 (m, 3H), 7.14–7.21 (m, 4H), 7.30–7.38 (m, 3H), 7.47–7.50 (m, 1H), 7.51–7.60 (m, 4H). ^{13}C ($CDCl_3$): 21.0, 52.5, 76.1, 114.1, 117.3, 120.2, 121.4, 122.4, 124.1, 124.4, 126.1, 127.1, 128.0, 128.5, 128.7, 129.3, 129.5, 130.4, 131.8, 137.5, 139.0, 144.0, 147.4. Anal. calcd. for $C_{29}H_{24}N_2S$: C, 80.52; H, 5.59; N, 6.48; found: C, 80.49; H, 5.60; N, 6.45.

4,10a-Bis(4-Chlorophenyl)-2-(4-methylphenyl)-1,10a-dihydro-2H-pyrazino[2,1-b][1,3]benzothiazole (2e)

Pale yellow solid from ethanol. ^1H ($CDCl_3$): 2.30 (s, 3H), 4.0 (d, 1H), 4.40 (d, 1H), 6.21–6.28 (m, 1H), 6.67 (s, 1H), 6.70–6.72 (m, 2H), 6.79–6.86 (m, 2H), 7.05–7.12 (m, 3H), 7.18–7.21 (m, 2H), 7.28–7.31 (m, 2H), 7.42–7.50 (m, 4H). ^{13}C ($CDCl_3$): 21.0, 52.3, 75.6, 114.1, 116.0, 117.7, 120.6, 121.7, 122.6, 124.1, 125.0, 126.3, 128.6, 128.8, 129.4, 130.5, 131.2,

132.3, 134.4, 135.7, 137.5, 143.6, 146.8. Anal. calcd. for $C_{29}H_{22}Cl_2N_2S$: C, 69.46; H, 4.42; N, 5.59; found: C, 69.51; H, 4.45; N, 5.57.

2,4,10a-Tris(4-methylphenyl)-1,10a-dihydro-2H-pyrazino[2,1-b][1,3]benzothiazole (2f)

White solid from ethanol. ^1H ($CDCl_3$): 2.24 (s, 3H), 2.30 (s, 3H), 2.35 (s, 3H), 4.01 (d, 1H), 4.4 (d, 1H), 6.24–6.30 (m, 1H), 6.65 (s, 1H), 6.70–6.82 (m, 4H), 7.0–7.10 (m, 5H), 7.11–7.18 (m, 2H), 7.42–7.50 (m, 4H). ^{13}C ($CDCl_3$): 20.96, 21.44, 21.50, 52.3, 76.2, 114.0, 117.3, 119.3, 121.2, 122.4, 124.0, 124.4, 126.0, 127.1, 129.3, 130.0, 130.3, 131.4, 132.2, 134.7, 135.8, 136.1, 138.2, 144.0, 147.4: Anal. calcd. for $C_{31}H_{28}N_2S$: C, 80.83; H, 6.13; N, 6.08; found: C, 80.85; H, 6.12; N, 6.11.

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