Simple Synthesis of Some Diphenylsulfapyrimidine Acetates from Chalcones and their Antimicrobial Activity

A. A. F. WASFY and A. A. ALY

Department of Chemistry, Faculty of Science, Benha University, Benha, Egypt
e-mail: wasfy588@hotmail.com

Received 14 August 2002

Since a very low yield (19—43 %) in the reported results on the cyclocondensation of sulfaguanidine acetate with chalcones was given, a careful reinvestigation was carried out. New series of chalcones, bearing electron-attracting groups in the aromatic moiety, have been used as precursors in the synthesis of diphenylsulfapyrimidine acetates with good yield. The compounds were tested for their biological properties.

The pyrimidine ring is part of many biologically active compounds. Several of pyrimidines have been successfully commercialized as pesticides or pharmaceuticals. For example, the sulfadiazine belongs to the class of sulfonamides drugs which are active against gram-positive and gram-negative bacteria [1], the activity is based on the intercalation with DNA and the formation of free radicals.

In the work recently reported by *Reisch et al.* [2], sulfaguanidine acetate had been condensed with chalcones, bearing electron-releasing groups, *e.g.* —OCH_3 or —OH in the aromatic moiety, in dimethyl sulfoxide at 110 ℃ to give diphenylsulfapyrimidine acetates in low yield. Prompted by these observations and in continuation of the work on synthesis of *N*-heterocycles utilizing chalcones as starting components [3, 4], it was considered worthwhile to reinvestigate the above reaction. In this investigation we sought to augment the reactivity of chalcones toward condensation with sulfaguanidine acetate by introducing electron-attracting groups, *e.g.* —NO_2 or chloro group in the aromatic moiety, in an attempt to improve the yield and quality of the products.

Thus, heating of 1,3-diaryl-2-propen-1-ones *Ia*—*In* with equal molar quantities of sulfaguanidine acetate *II* in the presence of dimethyl sulfoxide at 110 ℃ generates the desired structures *IIIa*—*IIIn* (Scheme 1) in yields between 42—86 %. Electron-withdrawing substituents R^1 like the nitro group enhance the reactivity, while the electron-releasing groups like the methoxy group lower it.

The structural assignments of the sulfapyrimidine acetates were based on characteristic IR, ^{1}H NMR spectral data as well as elemental analyses.

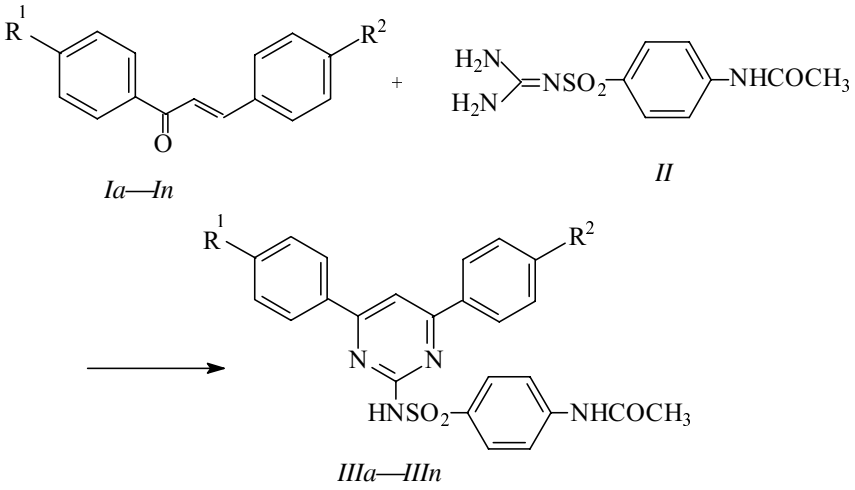
The infrared spectra of the sulfapyrimidine acetates *IIIa*—*IIIn* exhibited absorption bands in the region $\tilde{\nu}$ = 3285—3370 cm^{-1} attributable to the presence of bonded NH of both the amide (—NHCO—) and sulfonamido (—$NHSO_2$—) groups and in the region 1673—1688 cm^{-1} and also at 1600 cm^{-1} due to amide carbonyl functional group (band I and II). The strong absorption bands at 1375 cm^{-1} and 1150 cm^{-1} were due to the presence of sulfonyl group (—SO_2—). In the ^{1}H NMR spectra, the chemical shifts of *N*-acetyl, *O*-methyl, and Ar-methyl protons are characteristic at δ = 1.98—2.08, 3.82—3.90, and 2.22—2.27, respectively. The phenyl and the pyrimidine protons overlapped as multiplets at about δ = 6.80—8.30, while two protons were exchangeable with deuterium oxide in all cases due to the presence of NH protons.

The antimicrobial activity of synthesized derivatives was examined *in vitro* by the filter-paper disc method [5]. All compounds were tested for activity against gram-positive and gram-negative bacteria and selected fungi using sulfadiazine as a reference standard.

A qualitative screen was performed on all compounds while quantitative assays were done on active compounds only. The results are summarized in Table 1. The results reveal that all the compounds are weakly or moderately active except *IIIi*—*IIIn*. These compounds have fairly marked activity, indicating that combination of polar substituents like Cl, OCH_3, NO_2, OCH_3 or two NO_2 imparts enhanced antimicrobial activity. Compound *IIIn* had activity nearly comparable to commercial antibacterial agent, sulfadiazine.

EXPERIMENTAL

Melting points were taken in open capillary tubes and are uncorrected. IR spectra in KBr were recorded on a Shimadzu 470 spectrophotometer and ^{1}H NMR spectra in DMSO on a Jeol Fx 90 Q9 (Fourier trans-



Compound *I, III*	R^1	R^2	Yield/%
a	H	H	67 (68 [2])
b	CH_3	H	56
c	OCH_3	H	52
d	Cl	H	66
e	NO_2	H	81
f	CH_3	CH_3	50
g	OCH_3	CH_3	46
h	Cl	CH_3	58
i	NO_2	CH_3	75
j	CH_3	OCH_3	49
k	OCH_3	OCH_3	42 (43 [2])
l	Cl	OCH_3	54
m	NO_2	OCH_3	69
n	NO_2	NO_2	86

Scheme 1

form NMR spectrometer) using TMS as internal reference (chemical shifts are expressed as δ).

The starting compounds 1,3-diaryl-2-propen-1-ones *Ia—In* were prepared by the method of *Weygand* and *Strobelt* [6]. Also, the sulfaguanidine acetate *II* was prepared according to the published procedure [7], yield 60 %, m.p. = 259—261 °C (literature value 261—262 °C).

The following compounds were synthesized as described below. Their characterization data are reported in Ref. [2]: 4,6-Diphenylpyrimidine-2-sulfonamido-N^4-acetamide *IIIa* (67 %), m.p. = 241—243 °C, (Ref. [2] gives m.p. = 242—244 °C); 4,6-bis(4-anisyl)-pyrimidine-2-sulfonamido-N^4-acetamide *IIIk* (42 %), m.p. = 294—296 °C (Ref. [2] gives m.p. = 295—297 °C).

4,6-Diarylsulfapyrimidine Acetates (*IIIa—IIIn*)

To chalcone (0.005 mol) and sulfaguanidine acetate *II* (1.28 g; 0.005 mol), dry and distilled dimethyl sulfoxide (30 cm^3) was added. The mixture was warmed to complete dissolution and anhydrous potassium carbonate (5 g) was added in portions until solution became alkaline to litmus. The reaction mixture was boiled at 110 °C for 6 h, cooled and poured into 50 g of ice, stirred for 1 h and left to stand overnight. The mixture was filtered, and the filtrate acidified with dilute acetic acid (50 %). A yellow solid was usually collected which upon recrystallization from a hot mixture of water and ethanol gave the above acetates.

Table 1. Antimicrobial Activity (A) and Minimum Inhibitory Concentration (MIC/(mmol dm^{-3})) for Studied Compounds[a,b]

Compound	*Bacillus subtilis*		*Bacillus cereus*		*Escherichia coli*		*Aspergillus niger*		*Penicillium notatum*	
	A	{MIC}	A	{MIC}	A	{MIC}	A	{MIC}	A	{MIC}
IIIc	+	0.26	++	0.53	++	0.26	+	0.53	+	1.05
IIId	++	0.52	+	0.52	++	1.04	+	0.52	+	1.04
IIIe	++	0.51	++	0.51	++	0.26	+	1.02	++	0.51
IIIg	+	0.51	++	1.02	++	0.51	+	1.02	+	0.51
IIIh	++	0.25	++	0.51	++	0.25	+	0.51	++	0.51
IIIi	++	0.25	++	0.25	++	0.50	++	0.50	++	0.99
IIIj	+	0.51	++	1.02	++	0.51	+	1.02	+	0.51
IIIk	++	0.25	++	0.25	++	0.50	+	0.25	++	0.50
IIIl	+++	0.49	++	0.49	++	0.25	++	0.49	++	0.25
IIIm	++	0.24	+++	0.48	+++	0.48	++	0.24	++	0.24
IIIn	+++	0.23	+++	0.23	+++	0.46	++	0.46	++	0.23
Sulfadiazine	+++	0.50	+++	0.50	+++	1.00	++	0.50	+++	0.50

a) The width of the inhibition zone indicates the potency of activity (diameter of the zone/mm): + mild (1—7); ++ moderate (8—13); +++ marked (14—17). The results of control samples (showing negative response) are not included. *b*) Origin of cultures: Department of Botany, Faculty of Science, Benha University, Benha, Egypt.

4-(4-Tolyl)-6-phenylpyrimidine-2-sulfonamido-N^4-acetamide (*IIIb*)

1-(4-Tolyl)-3-phenyl-2-propen-1-one *Ib* (1.11 g) gave *IIIb*, 1.28 g (56 %), m.p. = 216—218 °C. IR spectrum, $\tilde{\nu}$/cm^{-1}: 3370 (NH), 1680 (amidic CO), 1620 (C═C), 1375, 1150 (SO_2); ^{1}H NMR spectrum, δ: 1.98 (s, 3H, N—acetyl), 2.22 (s, 3H, $CH_{3\,arom}$), 6.95—8.21 (m, 14H, H_{arom} and pyrimidine H-5 protons), 10.08 (s, 1H, NH, exchangeable with D_2O), 11.14 (br s, 1H, NH, exchangeable with D_2O). For $C_{25}H_{22}N_4O_3S$ w_i(calc.): 65.49 % C, 4.84 % H, 12.22 % N; w_i(found): 65.38 % C, 4.66 % H, 12.35 % N.

4-(4-Anisyl)-6-phenylpyrimidine-2-sulfonamido-N^4-acetamide (*IIIc*)

1-(4-Anisyl)-3-phenyl-2-propen-1-one *Ic* (1.19 g) gave *IIIc*, 1.23 g (52 %) as a colourless solid, m.p. = 224—226 °C. IR spectrum, $\tilde{\nu}$/cm^{-1}: 3350 (NH), 1675 (amidic CO), 1615 (C═C), 1380, 1165 (SO_2); ^{1}H NMR spectrum, δ: 2.05 (s, 3H, N—acetyl), 3.85 (s, 3H, OCH_3), 6.90—8.24 (m, 14H, H_{arom} and pyrimidine H-5 protons), 10.22 (s, 1H, NH, exchangeable with D_2O), 11.04 (br, s, 1H, NH, exchangeable with D_2O). For $C_{25}H_{22}N_4O_4S$ w_i(calc.): 63.28 % C, 4.67 % H, 11.81 % N; w_i(found): 63.46 % C, 4.80 % H, 11.75 % N.

4-(4-Chlorophenyl)-6-phenylpyrimidine-2-sulfonamido-N^4-acetamide (*IIId*)

1-(4-Chlorophenyl)-3-phenyl-2-propen-1-one *Id* (1.21 g) gave *IIId*, 1.58 g (66 %) as a colourless solid, m.p. = 238—240 °C. IR spectrum, $\tilde{\nu}$/cm^{-1}: 3340 (NH), 1685 (amidic CO), 1625 (C═C), 1370, 1160 (SO_2); ^{1}H NMR spectrum, δ: 2.02 (s, 3H, N—acetyl), 7.04—8.18 (m, 14H, H_{arom} and pyrimidine H-5 protons), 10.20 (s, 1H, NH, exchangeable with D_2O), 11.90 (br s, 1H, NH, exchangeable with D_2O). For $C_{24}H_{19}ClN_4O_3S$ w_i(calc.): 60.19 % C, 4.00 % H, 11.70 % N; w_i(found): 60.31 % C, 4.22 % H, 11.94 % N.

4-(4-Nitrophenyl)-6-phenylpyrimidine-2-sulfonamido-N^4-acetamide (*IIIe*)

1-(4-Nitrophenyl)-3-phenyl-2-propen-1-one *Ie* (1.27 g) gave *IIIe*, 1.98 g (81 %) as a pale yellow solid, m.p. = 270—272 °C. IR spectrum, $\tilde{\nu}$/cm^{-1}: 3310 (NH), 1688 (amidic CO), 1630 (C═C), 1367, 1154 (SO_2); ^{1}H NMR spectrum, δ: 2.06 (s, 3H, N—acetyl), 7.12—8.26 (m, 14H, H_{arom} and pyrimidine H-5 protons), 10.24 (s, 1H, NH, exchangeable with D_2O), 12.00 (br, s, 1H, NH, exchangeable with D_2O). For $C_{24}H_{19}N_5O_5S$ w_i(calc.): 58.89 % C, 3.91 % H, 14.31 % N; w_i(found): 58.98 % C, 4.06 % H, 14.28 % N.

4,6-Bis(4-tolyl)pyrimidine-2-sulfonamido-N^4-acetamide (*IIIf*)

1,3-Bis(4-tolyl)-2-propen-1-one *If* (1.18 g) gave *IIIf*, 1.18 g (50 %) as a colourless solid, m.p. = 222—224 °C. IR spectrum, $\tilde{\nu}$/cm^{-1}: 3365 (NH), 1673 (amidic CO), 1618 (C═C), 1365, 1145 (SO_2); ^{1}H NMR spectrum, δ: 2.00 (s, 3H, N—acetyl), 2.24 (s, 6H, 2 × $CH_{3\,arom}$), 6.80—8.09 (m, 13H, H_{arom} and pyrimidine H-5 protons), 10.30 (s, 1H, NH, exchangeable with D_2O), 11.50 (br s, 1H, NH, exchangeable with D_2O). For $C_{26}H_{24}N_4O_3S$ w_i(calc.): 66.08 % C, 5.12 % H, 11.86 N; w_i(found): 66.28 % C, 5.24 % H, 11.75 % N.

4-(4-Anisyl)-6-(4-tolyl)pyrimidine-2-sulfonamido-N^4-acetamide (*IIIg*)

1-(4-Anisyl)-3-(4-tolyl)-2-propen-1-one *Ig* (1.26 g) gave *IIIg*, 1.12 g (46 %) as a colourless solid, m.p. = 234–236 °C. IR spectrum, $\tilde{\nu}/\mathrm{cm}^{-1}$: 3320 (NH), 1679 (amidic CO), 1628 (C=C), 1378, 1152 (SO_2); ^{1}H NMR spectrum, δ: 2.08 (s, 3H, N—acetyl), 2.22 (s, 3H, $CH_{3\,\mathrm{arom}}$), 3.90 (s, 3H, OCH_3), 6.94—8.15 (m, 13H, H_{arom} and pyrimidine H-5 protons), 10.18 (s, 1H, NH, exchangeable with D_2O), 11.80 (br s, 1H, NH, exchangeable with D_2O). For $C_{26}H_{24}N_4O_4S$ w_i(calc.): 63.92 % C, 4.95 % H, 11.47 % N; w_i(found): 63.78 % C, 4.74 % H, 11.64 % N.

4-(4-Chlorophenyl)-6-(4-tolyl)pyrimidine-2-sulfonamido-N^4-acetamide (*IIIh*)

1-(4-Chlorophenyl)-3-(4-tolyl)-2-propen-1-one *Ih* (1.28 g) gave *IIIh*, 1.43 g (58 %) as a colourless solid, m.p. = 245—247 °C. IR spectrum, $\tilde{\nu}/\mathrm{cm}^{-1}$: 3295 (NH), 1677 (amidic CO), 1626 (C=C), 1450, 1120 (SO_2); ^{1}H NMR spectrum, δ: 2.03 (s, 3H, N—acetyl), 2.21 (s, 3H, $CH_{3\,\mathrm{arom}}$), 6.88—8.08 (m, 13H, H_{arom} and pyrimidine H-5 protons), 10.35 (s, 1H, NH, exchangeable with D_2O), 11.45 (br s, 1H, NH, exchangeable with D_2O). For $C_{25}H_{21}ClN_4O_3S$ w_i(calc.) 60.91 % C, 4.30 % H, 11.36 % N; w_i(found): 61.08 % C, 4.42 % H, 11.48 % N.

4-(4-Nitrophenyl)-6-(4-tolyl)pyrimidine-2-sulfonamido-N^4-acetamide (*IIIi*)

1-(4-Nitrophenyl)-3-(4-tolyl)-2-propen-1-one *Ii* (1.34 g) gave *IIIi*, 1.89 g (75 %) as a pale yellow solid, m.p. = 280—282 °C. IR spectrum, $\tilde{\nu}/\mathrm{cm}^{-1}$: 3295 (NH), 1674 (amidic CO), 1629 (C=C), 1355, 1140 (SO_2); ^{1}H NMR spectrum, δ: 1.99 (s, 3H, N—acetyl), 2.27 (s, 3H, $CH_{3\,\mathrm{arom}}$), 6.99—8.25 (m, 13H, H_{arom} and pyrimidine H-5 protons), 10.44 (s, 1H, NH, exchangeable with D_2O), 11.98 (br s, 1H, NH, exchangeable with D_2O). For $C_{25}H_{21}N_5O_5S$ w_i(calc.): 59.63 % C, 4.20 % H, 13.91 % N; w_i(found): 59.71 % C, 4.40 % H, 13.76 % N.

4-(4-Tolyl)-6-(4-anisyl)pyrimidine-2-sulfonamido-N^4-acetamide (*IIIj*)

1-(4-Tolyl)-3-(4-anisyl)-2-propen-1-one *Ij* (1.26 g) gave *IIIj*, 1.20 g (49 %) as a colourless solid, m.p. = 236—238 °C. IR spectrum, $\tilde{\nu}/\mathrm{cm}^{-1}$: 3330 (NH), 1682 (amidic CO), 1619 (C=C), 1330, 1130 (SO_2); ^{1}H NMR spectrum, δ: 2.07 (s, 3H, N—acetyl), 2.23 (s, 3H, $CH_{3\,\mathrm{arom}}$), 3.83 (s, 3H, OCH_3), 7.04—8.30 (m, 13H, H_{arom} and pyrimidine H-5 protons), 10.50 (s, 1H, NH, exchangeable with D_2O), 11.60 (br s, 1H, NH, exchangeable with D_2O). For $C_{26}H_{24}N_4O_4S$ w_i(calc.): 63.92 % C, 4.95 % H, 11.47 % N, w_i(found): 64.04 % C, 5.22 % H, 11.29 % N.

4-(4-Chlorophenyl)-6-(4-anisyl)pyrimidine-2-sulfonamido-N^4-acetamide (*IIIl*)

1-(4-Chlorophenyl)-3-(4-anisyl)-2-propen-1-one *Il* (1.36 g) gave *IIIl*, 1.37 g (54 %) as a colourless solid, m.p. = 303—305 °C. IR spectrum, $\tilde{\nu}/\mathrm{cm}^{-1}$: 3290 (NH), 1681 (amidic CO), 1624 (C=C), 1420, 1170 (SO_2); ^{1}H NMR spectrum, δ: 2.04 (s, 3H, N—acetyl), 3.87 (s, 3H, OCH_3), 6.95—8.19 (m, 13H, H_{arom} and pyrimidine H-5 protons), 10.21 (s, 1H, NH, exchangeable with D_2O), 11.30 (br s, 1H, NH, exchangeable with D_2O). For $C_{25}H_{21}ClN_4O_4S$ w_i(calc.): 59.00 % C, 4.16 % H, 11.01 % N; w_i(found): 59.20 % C, 4.30 % H, 11.22 % N.

4-(4-Nitrophenyl)-6-(4-anisyl)pyrimidine-2-sulfonamido-N^4-acetamide (*IIIm*)

1-(4-Nitrophenyl)-3-(4-anisyl)-2-propen-1-one *Im* (1.42 g) gave *IIIm*, 1.79 g (69 %) as a pale yellow solid, m.p. = 314—316 °C. IR spectrum, $\tilde{\nu}/\mathrm{cm}^{-1}$: 3318 (NH), 1678 (amidic CO), 1622 (C=C), 1410, 1100 (SO_2); ^{1}H NMR spectrum, δ: 2.01 (s, 3H, N—acetyl), 3.82 (s, 3H, OCH_3), 6.92—8.16 (m, 13H, H_{arom} and pyrimidine H-5 protons), 10.15 (s, 1H, NH, exchangeable with D_2O), 11.28 (br s, 1H, NH, exchangeable with D_2O). For $C_{25}H_{21}N_5O_6S$ w_i(calc.): 57.80 % C, 4.07 % H, 13.48 % N; w_i(found): 57.68 % C, 4.27 % H, 13.29 % N.

4,6-Bis(4-nitrophenyl)pyrimidine-2-sulfonamido-N^4-acetamide (*IIIn*)

1,3-Bis(4-nitrophenyl)-2-propen-1-one *In* (1.49 g) gave *IIIn*, 2.30 g (86 %) as a pale yellow solid, m.p. = 320—322 °C. IR spectrum, $\tilde{\nu}/\mathrm{cm}^{-1}$: 3315 (NH), 1674 (amidic CO), 1627 (C=C), 1370, 1118 (SO_2); ^{1}H NMR spectrum, δ: 2.00 (s, 3H, N—acetyl), 6.98—8.22 (m, 13H, H_{arom} and pyrimidine H-5 protons), 10.10 (s, 1H, NH, exchangeable with D_2O), 11.40 (br s, 1H, NH, exchangeable with D_2O). For $C_{24}H_{18}N_6O_7S$ w_i(calc.): 53.93 % C, 3.39 % H, 15.72 % N; w_i(found): 53.78 % C, 3.48 % H, 15.69 % N.

Antimicrobial Activity

The culture medium was normal nutrient agar supplemented with yeast solution of the concentration 1 g/cm^3. According to the solubility of the tested compounds, different polar and nonpolar solvents were used; good solubility was found in 10 vol. % acetone for all the tested compounds. Based on the previous preliminary test, closely spaced test concentrations were selected; they are 500 μg dm^{-3}, 250 μg dm^{-3}, and 125 μg dm^{-3}.

Sulfadiazine was dissolved in filter-sterilized 10 cm^3 of 10 vol. % acetone and employed in similar concentration as control.

Acknowledgements. The authors are grateful to Dr. M. Amer, Department of Botany, Faculty of Science, Benha University, for biological evaluation.

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