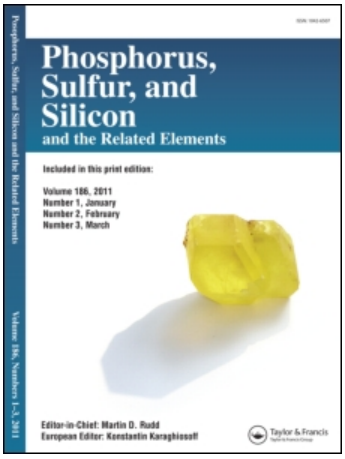

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Studies on Organophosphorus Compounds XIII[1, 2]: Efficient Synthesis of Polyfunctionally Substituted Heterocycles by the Utility of Phosphonium Salts

Nadia R. Mohamed[a]; Mervat M. Abdel Halim[b]; Wafaa A. Gad[a]; Mohamed F. Zaid[a]
[a] Photochemistry Department, National Research Center, Giza, Egypt [b] Hormones Department, National Research Center, Giza, Egypt

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Nadia R. Mohamed
Photochemistry Department, National Research Center, Giza, Egypt

Mervat M. Abdel Halim
Hormones Department, National Research Center, Giza, Egypt

Wafaa A. Gad
Mohamed F. Zaid
Photochemistry Department, National Research Center, Giza, Egypt

*We describe in this article the interaction of phosphonium salts **3a–c** with thioanilide potassium salt **2** to produce the corresponding pyridinone derivatives **6,8** and thiophene derivative **10**, respectively. The interaction of thioanilide salt **12** with phosphonium salts **3a,c–e** led to the formation of the corresponding thiophene derivatives **14a–d**. On the other hand, the reaction of androstan derivative **15** with phenyl isothiocyanate and phosphonium salt **3c** produced the thiophene derivative **18**. Studying the behavior of androstan derivative **15** toward Wittig reagents **19a,b** afforded the corresponding product **21** via the intermediate **20**. The in vitro–biological activity of some newly synthesized compounds against gram-positive and gram-negative bacteria was studied.*

Keywords Benzoxazol-2-ylethanenitrile; hormones; phenyl isothiocyanate; phosphonium salts; thiophene

INTRODUCTION

Since its development, the Wittig reaction has remained one of the best routes for the construction of carbon–carbon double bonds.[3] The Wittig reagent needed for the reaction is prepared by deprotonation of the corresponding phosphonium salt generated by quaternization of a phosphine with organic halides.[4] In continuation of our previous work on the reactions of Wittig reagents,[5–7] we would like in this article to report the

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Address correspondence to Nadia R. Mohamed, Photochemistry Department, National Research Center, Chemical Industries Research Division, El-Tahrir St., Dokki, Giza, 12622, Egypt. E-mail: nadia_ragab_m@hotmail.com

behavior of phosphonium salts toward potassium thioanilide salts for the synthesis of different bioactive polyfunctionally substituted heterocycles. Potassium thioanilide salts generated via the interaction of thiocyanates with active methylenes[8] were previously utilized for the formation of polyfunctionally substituted thiophene,[8,9] dihydrothiazoles,[10] and thiazolidines.[11] In this article, we report a facile synthesis of pyridinone, thiophene, and pyridazinoandrostan derivatives via the interaction of thioanilide salts with different phosphonium salts.

DISCUSSION

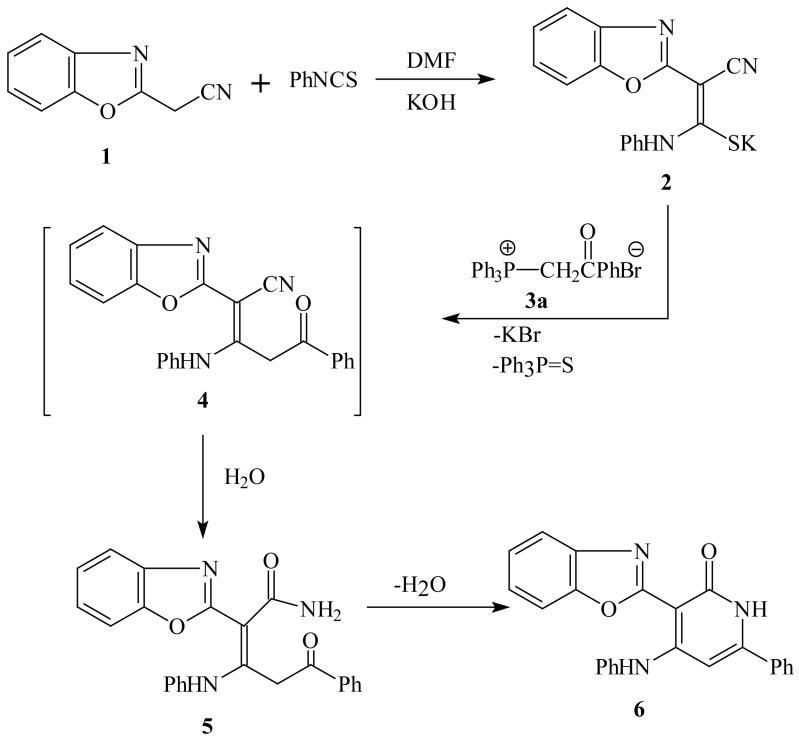
2-benzoxazol-2-ylethanenitrile **1** reacted with phenyl isothiocyanate in dry N,N-dimethyl formamide containing potssium hydroxide at r.t. to produce nonisolable potassium thioanilide **2**.[8] The treatment of **2** with phosphonium salt **3a** afforded the pyridinone derivative **6**. Confirmation of the structure of **6** is based on the following:

1. Elemental analysis of compound 6 revealed the absence of sulfur and was in accordance with the suggested structure.
2. The IR spectrum of this compound revealed the absence of any signal characteristic to the nitrile group, which appeared at 2174 cm^{-1} in the spectrum of compound **1**. It showed bands at 3244 (NH), 1681 (C=O), and 1604 (C=N).
3. The ^1H NMR of compound 6 showed a signal (singlet) at 4.85 for one proton (CH pyridine proton); multiplets at 6.70–7.35, 7.40–7.85, and 7.91–8.25 for 15 protons (aromatic protons and NH); and a singlet at $\delta = 12.30$ (1H, NH).

The formation of compound **6** may proceed via the addition of phosphonium salt **3a** to potassium thioanilide **2** to produce intermediate **4** by a loss of triphenylphosphine sulfide. The latter was hydrolized to form **5,** which cyclized and aromatized to afford the final pyridinone derivative **6** (Scheme 1).

To generallize this methodology, thioanilide salt **2** was allowed to react with triphenylvinylphosphonium bromide salt under the same previous condition. The isolated product in this case was formulated as the pyridinone derivative **8** (Scheme 2). The structure of the latter was confirmed according to the analytical and spectral data (cf. Experimental section).

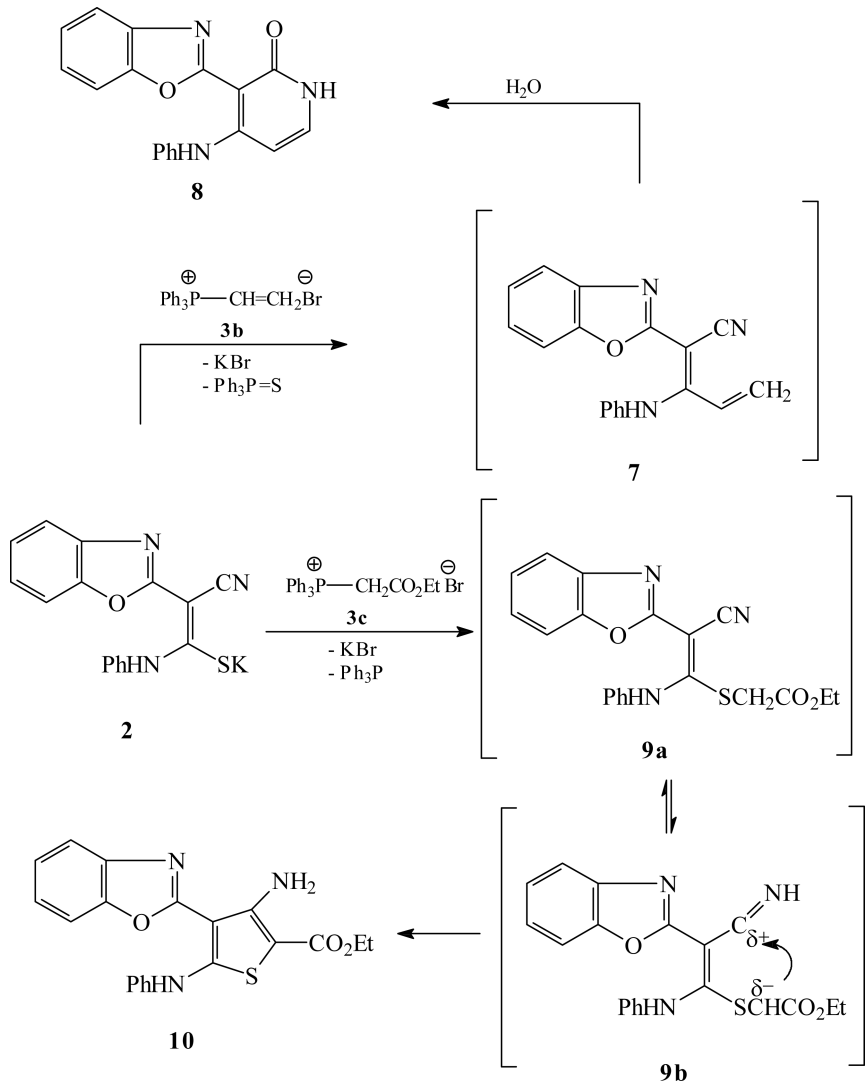
On the other hand, reaction of thioanilide salt **2** with phosphonium salt **3c** led to the formation of thiophene derivative **10**. This compound may be formed via the addition of phosphonium salt **3c** with the elimination of KBr and triphenyl phosphine to produce intermediate **9a**.



SCHEME 1

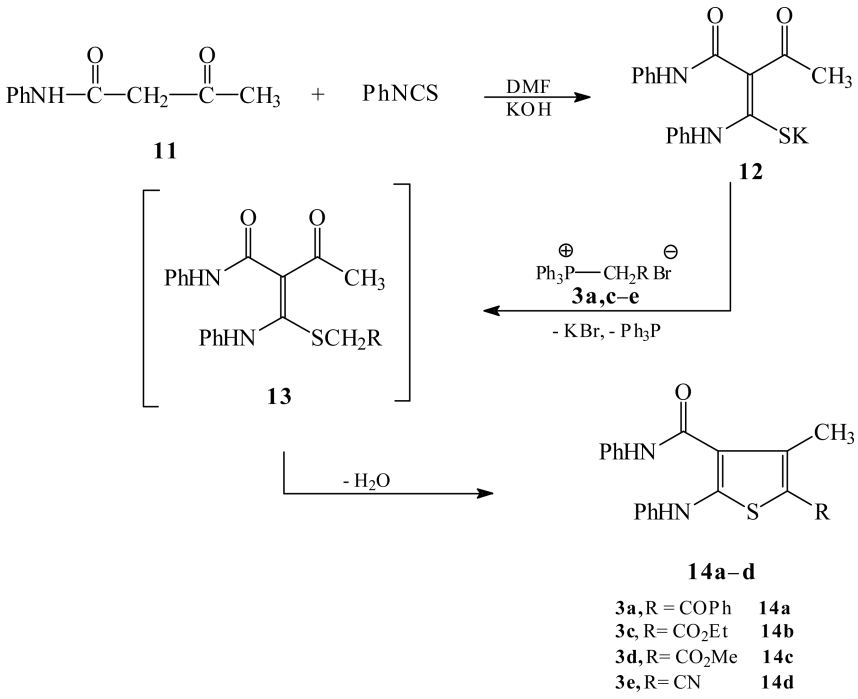
The latter was isomerized to afford **9b** that eventually cyclized, forming adduct **10** (Scheme 2). All the microanalytical and spectroscopic data of compound **10** were in accordance with its structure (cf. Experimental section).

Next, we studied the previous phenomena on other types of active methylene compounds. Acyclic thioanilide potassium salt **12** generated from the reaction of acetoacetanilide with isothiocyanate in the presence of KOH was allowed to react with phosphonium salts **3a**,**c–e** to produce the corresponding thiophene derivatives **14a–d** (Scheme 3). The mass spectrum of **14b** taken as an example revealed the presence of a molecular ion peak at m/z = 380 [M^+]. IR spectra of **14b** showed the presence of bands at 3235 (NH), 2924 (CH_3), 1735, and 1679 (2C=O). Its ^{1}H NMR spectrum showed the characteristic quartet and triplet pattern for the ethyl group at $\delta = 3.75$ and 1.18 ppm respectively. It revealed also a singlet at 2.65 (3H, CH_3), two multiplets at $\delta = 6.85$–7.45 and 7.60–7.95 (11H, 10 aromatic proton, and NH), and a singlet at 11.45 for NH proton.



SCHEME 2

Similarly, all the microanalytical and spectroscopic data of compounds **14a–d** were incompitable with their structures (cf. Experimental section). The production of **14** may have occurred via the addition of the phosphonium salt to the thioanilide salt **12** to form **13** with a loss of KBr and triphenyl phosphine. The cyclization of **13** with the elimination of water produced the final isolated product **14** (Scheme 3).

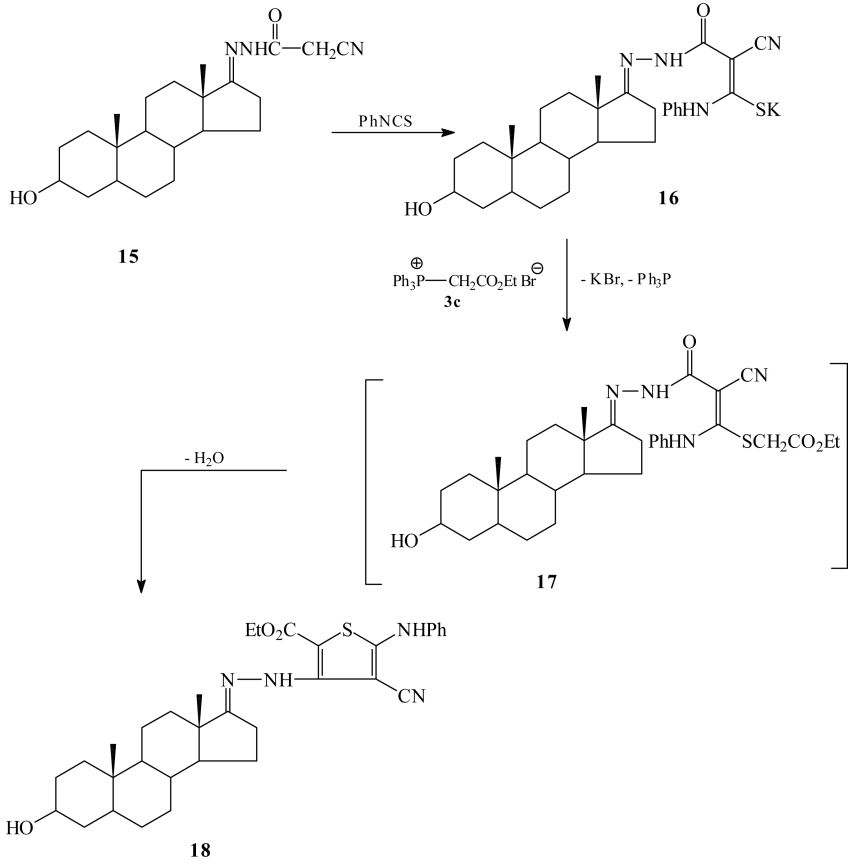


SCHEME 3

In continuation of our previous work on the behavior of phosphorus reagents toward steriods,[12,13] we would like to report here the effect of phosphonium salt **3c** and Wittig reagents **19a**,**b** on 3β-hydroxy-5α-androstan-17-cyanoacetylhydrazone (**15**).[14]

When phenyl isothiocyanate was added to androstan derivative **15** in N,N-dimethylformamide containing KOH, the corresponding potassium thioanilide salt **16** was formed. The latter was reacted with the phosphonium salt **3c** to yield the thiophene derivative **18** via the intermediate **17** (Scheme 4). The IR spectra of **18** revealed the absence of the characteristic band of the cyanide group and the appearance of bands at 3455 for (OH), 3241 (NH), 2970 (CH_3), 2170 (CN), 1732 (ester CO), and 1687 NHCO. ^{1}H NMR and microanalytical data were in accordance with structure **18** (cf. Experimental section).

The interaction of androstan derivative **15** with Wittig reagent **19a**,**b** in dry toluene led to the formation of the product **21**. The formation of compound **21** may occur via the addition of a Wittig reagent to the carbonyl group with a loss of triphenylphosphinoxide to afford intermediate **20**. The cyclization of compound **20** with the elemination of

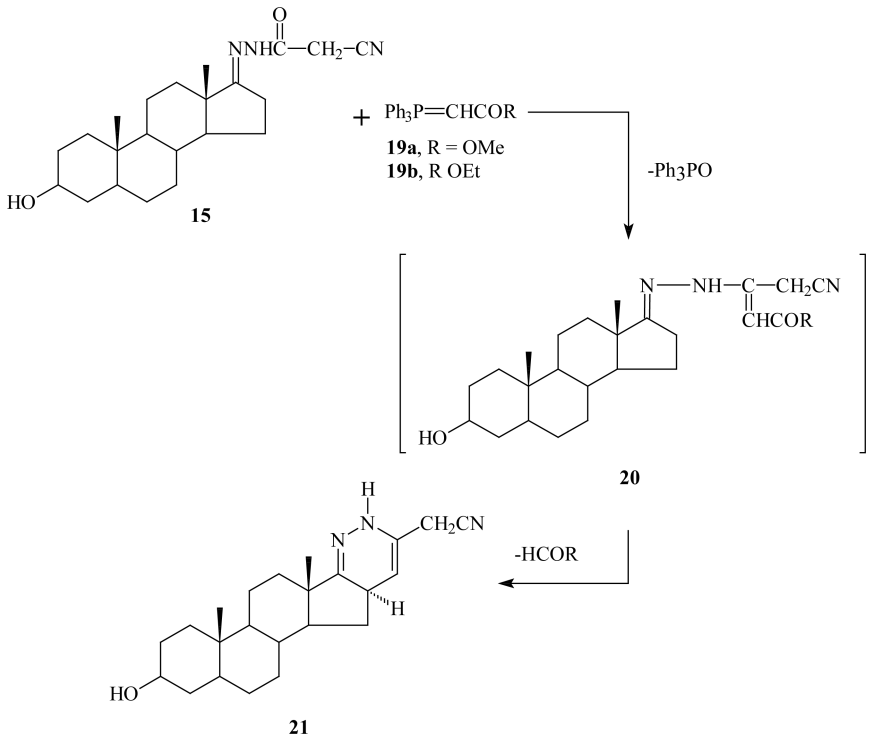


SCHEME 4

alkyl formate produced the final product **21** (Scheme 5). The microanalytical and spectroscopic data supported the proposed structure (c.f. Experimental section).

BIOACTIVITY

The in vitro–antimicrobial activity of the newly prepared compounds **6**, **8**, **18**,**21** against two groups of microorganisms, including three strains of gram-positive bacteria and three strains of gram-negative bacteria, was investigated in comparison with ampicillin. The four tested compounds were capable of inhibiting the growth of both gram-positive and gram-negative bacteria, and they could be considered as promising



SCHEME 5

antimicrobial agents. Table I shows the results of the bioassay. In conclusion, we have reported here the importance of the tested compounds as antibacterial agents. Further studies should be made to elucidate their mechanism of action.

EXPERIMENTAL

All melting points are uncorrected. The appropriate precautions in handling sensitive compounds were taken. IR spectra were recorded in KBr with Pa 9712 IR spectrometer. The ^{1}H NMR spectrum were run in $CDCl_3$ and DMSO using TMS as an internal reference on a varian EM-360 (60 MHz). The MS were taken on a kratos (75 ev) MS spectrometer. Elemental analyses were carried out by the Microanalytical Center, National Research Center, Giza, Egypt. The biological activity of the new compounds were tested at the Analytical Center, Cairo University. The described results using steriods showed the characterestic

TABLE I Antimicrobial Potentialities of the Tested Compounds Expressed as Size (mm/mg Sample) of Inhibition Zone

		Compounds				
Test Organisms		**6**	**8**	**18**	**21**	Ampicillin
1	*Bacillus subtilis*	14	12	13	15	+
2	*Staphylococcus aureus*	16	15	14	15	+
3	*Streptococcus faeculis*	15	13	13	13	+
4	*Escherichia coli*	15	16	13	14	+
5	*Neisseria genorrhes*	16	15	12	14	+
6	*Pseudomonae aeruginosa*	16	14	13	14	+

spectral data of the cyclopentano-perhydrophenanthrene moiety of steriods similar to those reported in the literature.[15,16]

Reaction of Thioanilide Potassium Salt 2 with Phosphonium Salts 3a–c: General Procedure

A mixture of 2-benzoxazol-2-ylethanenitrile **1** (0.01 mol), potassium hydroxide (0.56 g, 0.01 mol), and phenyl isothiocyanate (1.35 g, 0.01 mol) in dry N,N-dimethylformamide (10 mL) was stirred at r.t. for 2 h, and then each of the phosphonium salts **3a–c** (0.01 mol) was added. The reaction mixture was stirred for a further 8 h and poured into ice water with a few drops of HCl. The solid precipitate was collected by filtration, dried, and crystallized from the proper solvent.

4-Anilino-(1,3-benzoxazol-2-yl)-6-phenyl-1H-pyridin-2-one 6

Compound **6** is yellow, cryst., solvent: ethanol, yield: 2.84 g, 75%, m.p. = 149°C. IR (KBr) $\nu = 3244$ (NH), 1681 (C=O), 1604 (C=N) cm^{-1}, ^1H NMR (DMSO): $\delta = 4.85$ (s, 1H, pyridinone CH), 6.70–7.35 (m, 5H, aromatic protons), 7.40–7.85 (m, 5H, aromatic protons), 7.91–8.25 (m, 5H, 4 aromatic protons and NH), 12.30 (s, 1H, NH). MS: m/z = 379 [M^+], 363 [M^+-O], 303 [M^+-Ph]. Found: C, 75.81; H, 14.48; N, 11.00; $C_{24}H_{17}N_3O_2$ (379.41); required: C, 75.97; H, 4.52; N, 11.08.

4-Anilino-3-(1,3-benzoxazol-2-yl)-1H-pyridin-2-one 8

Compound **8** is yellow ppt, cryst., solvent: benzene, yield: 2.18 g, 72%, m.p. = 112°C. IR (KBr) $\nu = 3243$ (NH), 1679 (C=O), 1601 (C=N), ^1H NMR (DMSO): $\delta = 2.85$ (m, 1H, CH), 3.80 (d, 1H, CH), 6.90–7.40 (m,

6H, aromatic protons, NH), 7.65–7.95 (m, 4H, aromatic protons), 12.30 (s, 1H, NH). MS: m/z = 303 [M^+] Found: C, 71.00; H, 4.25; N, 3.74; $C_{18}H_{13}N_3O_2$ (303.31); required: C, 71.28; H, 4.32; N, 3.85.

Ethyl-3-amino-5-anilino-4-(1,3-benzoxazol-2-yl)-thiophene-2-carboxylate 10

Compound **10** is yellow, cryst., solvent: benzene, yield: 2.95 g, 78%, m.p. = 185°C. IR (KBr) ν = 3420 (NH_2), 3240 (NH), 1732 (C=O), 1604 (C=N) cm^{-1}, ^1H NMR (DMSO): δ = 1.07 (t, 3H, CH_3), 4.05 (q, 2H, CH_2), 7.12–7.65 (m, 5H, aromatic protons), 7.73–7.80 (m, 4H, aromatic protons), 9.76 (s, 1H, NH), 11.22 (br.s, 2H, NH_2). MS: m/z = 379 [M^+]. Found: C, 63.11; H, 4.32; N, 11.00; S, 8.31; $C_{20}H_{17}N_3O_3S$ (379.43); required: C, 63.31; H, 4.52; N, 11.07; S, 8.45.

Reaction of Thioanilide Potassium salt 12 with Phosphonium Salts 3a,c–e, General Procedure

A mixture of acetoacetanilide (**11**) (0.01 mol), potassium hydroxide (0.56 g, 0.01 mol), and phenyl isothiocyanate (1.35 g, 0.01 mol) in dry N,N-dimethyl formamide (20 mL) was stirred for 6 h; then the appropriate phosphonium salts **3a**,**c–e** (0.01 mol) were added. Stirring was continued overnight, and then the reaction mixture was diluted with water (10 mL). The solid precipitated was collected by filtration, washed with water, dried, and crystallized from the proper solvent.

2-Anilino-5-benzoyl-4-methyl-N-phenyl-thiophene-3-carboxylate 14a

Compound **14a** is yellow ppt., cryst., solvent: benzene-n-hexane, yield: 2.14 g, 52%, m.p. = 82°C. IR (KBr) ν = 3210 (NH), 2949 (CH_3), 1690 (C=O), 1676 (C=O); ^1H NMR (DMSO): δ = 2.22 (s, 3H, CH_3), 7.15–7.70 (m, 5H, aromatic protons), 7.75–8.10 (m, 10H, aromatic protons), 10.25 (s, 1H, NH), 11.85 (s, 1H, CO-NH). MS: m/z = 412 [M^+]. Found: C, 72.18; H, 4.79; N, 6.28; S, 7.66; $C_{25}H_{20}N_2O_2S$ (412.50); required: C, 72.79; H, 4.89; N, 6.79; S, 7.77.

Ethyl-5-anilino-4-(anilino carbonyl)-3-methyl-thiophene-2-carboxylate 14b

Compound **14b** is yellow, cryst., solvent: $CHCl_3$ n-hexane, yield: 2.09 g, 55%, m.p. = 82°C. IR (KBr) ν = 3235 (NH), 2924 (CH_3), 1735 (C=O), 1679 (C=O); ^1H NMR (DMSO): δ = 1.18 (t, 3H, CH_3), 2.65 (s, 3H, CH_3),

3.75 (q, 2H, CH_2) 6.85–7.45 (m, 5H, aromatic protons), 7.60–7.95 (m, 6H, aromatic protons and NH), 11.45 (s, 1H, NH). MS: m/z = 380 [M^+] Found: C, 66.10; H, 5.00; N, 7.21; S, 8.11; $C_{21}H_{20}N_2O_3S$ (380.46); required: C, 66.29; H, 5.30; N, 7.36; S, 8.43.

Methyl-5-anilino-4-(anilino carbonyl)-3-methyl-thiophene-2-carboxylate 14c

Compound **14c** is yellow, cryst., solvent: benzene-n-hexane, yield: 1.86 g, 51%, m.p. = 72°C. IR (KBr) ν = 3220 (NH), 2945 (CH_3), 1730 (C=O), 1685 (CO); ^{1}H NMR (DMSO): δ = 1.80 (s, 3H, CH_3), 2.29 (s, 3H, CH_3), 6.85–7.55 (m, 5H, aromatic protons), 7.60–7.95 (m, 5H, aromatic protons), 9.75 (s, 1H, NH), 10.95 (s, 1H, NH). MS: m/z = 366 [M^+] Found: C, 65.49; H, 4.91; N, 7.56; S, 8.72; $C_{20}H_{18}N_2O_3S$ (366.435); required: C, 65.55; H, 4.95; N, 7.64; S, 8.75.

2-Anilino-5-cyano-4-methyl-N-phenyl-thiophene-3-carboxylate 14d

Compound **14d** is yellow, cryst., solvent: benzene-pet., ether 40–60°C; yield: 1.86 g, 56%, m.p. = 88°C. IR (KBr) ν = 2240 (NH), 2948 (CH_3), 2168 (CN), 1677 (C=O); ^{1}H NMR (DMSO): δ = 2.25 (s, 3H, CH_3), 6.90–7.45 (m, 5H, aromatic protons), 7.52–7.90 (m, 5H, aromatic protons), 9.70 (s, 1H, NH), 11.00 (s, 1H, NH). MS: m/z = 333 [M^+]. Found: C, 68.29; H, 4.33; N, 12.48; S, 9.61; $C_{19}H_{15}N_3OS$ (333.40); required: C, 68.45; H, 4.53; N, 12.60; S, 9.62.

Reaction of Androstan Derivative 15 with Phenyl Isothiocyanate and Phosphonium Salt 3c

To a solution of androstan derivative **15** (0.01 mol) in DMF (20 mL), phenyl isothiocyanate (1.35 g, 0.01 mol) was added. The reaction mixture was stirred for 2 h, and then phosphonium salt **3c** was added. Stirring was continued overnight, and the reaction was diluted with cold water (20 mL). The solid ppt was collected by filteration, dried, and crystallized from a suitable solvent.

3β-hydroxy-[ethyl-1′-anilino-3′-cyano-4′-hydrazo-thiophene-5-carboxylate]-17-androstane 18

Compound **18** is yellow, cryst., solvent: benzene, yield: 4.36 g, 76%, m.p. = 210°C. IR (KBr) ν = 3455 (OH), 3241 (NH), 2970 (CH_3), 2170 (CN), 1732 (CO), 1687 (C=O); ^{1}H NMR (DMSO): δ = 0.75 (s, 3H, 19-CH_3), 0.83

(s, 3H, CH_3), 1.20 (t, 3H, CH_3), 4.45 (q, 2H, CH_2), 7.40–8.20 (m, 6H, 5 aromatic protons and NH), 10.70 (s, 1H, OH), 10.85 (s, 1H, NH). MS: m/z = 574 [M^+]. Found: C, 68.88; H, 7.25; N, 9.71; S, 5.49; $C_{33}H_{42}N_4O_3S$ (574.77); required: C, 68.96; H, 7.37; N, 9.75; S, 5.58.

Reaction of Androstan Derivative 15 with Wittig Reagent 19a,b

A mixture of androstan derivative **15** (0.01 mol) and each one of Wittig reagent **19a**,**b** (0.01 mol) in toluene (30 mL) was heated under reflux for 5 h. The solvent was evaporated under vaccum. The remaining residue was washed several times with hot pet. ether (60–80°C) to remove triphenylphosphine oxide (TPPO). The product was then crystallized from benzene.

3β-hydroxy-2′-hydro-3′-acetonitrile-pyridazino[5′,6′-16,17]-5-α-androstan 21

Compound **21** is white, cryst., solvent: benzene, yield: 2.89 g, 79%, m.p. = 252°C. IR (KBr) ν = 3420 (OH), 3245 (NH), 2975 (CH_3), 2210 (CN); ^{1}H NMR (DMSO): δ = 0.76 (s, 3H, CH_3), 0.83 (s, 3H, CH_3), 3.18 (m, 1H, $C_3 - \alpha$H), 4.60 (s, 2H, CH_2CN), 7.22 (d, 1H, pyridazine $C_{4'}$H), 9.54 (s, 1H, OH). MS: m/z = 367 [M^+] Found: C, 75.00; H, 8.81; N, 11.22; $C_{23}H_{33}N_3O$ (367.52); required: C, 75.16; H, 9.05; N, 11.43.

Bioassay: Measurement of Antimicrobial Activity Using the Diffusion Disc Method

A filter-paper sterilized disc saturated with a measured quantity of the sample was placed on a plate containing a solid bacterial medium (nutrient agar broth), which was heavily seeded with the spore suspension of the tested organism. After inoculation, the diameter of the clear zone of inhibition surrounding the sample was taken as a measure of the inhibitory power of the sample against the particular test organism.[15–17]

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