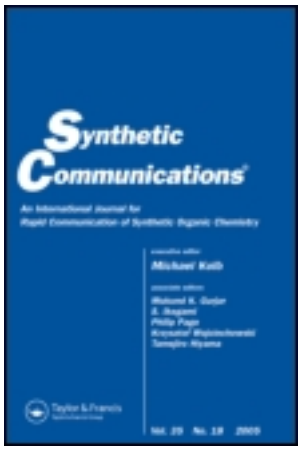

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Reactivity of Functionally Substituted Azoles Towards Electrophiles. Novel Synthesis of Thienylazoles and Phenylazoles

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Reactivity of Functionally Substituted Azoles Towards Electrophiles. Novel Synthesis of Thienylazoles and Phenylazoles

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ABSTRACT

Phenacyl bromide reacted with imidazole **1a** and 1,2,4-triazole **1b** to yield the respective azolylacetophenones **1c**,**d**. These reacted with phenyl isothiocyanate and phenacyl bromide yielding thienylazoles **4a**,**b**. Reaction of **1c**,**d** with dimethylformamide dimethylacetal followed by treating of the product with thiourea afforded the azolylpyrimidines **10a**,**b**. Azolylpyrans **8a**,**b** were obtained from reaction of **1c**,**d** with acrylonitrile. The reaction of azoles **1a**,**b** with chloroacetylacetone in acetone solution in the presence of base afforded the phenylazoles **13a**,**b**.

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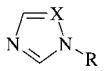
INTRODUCTION

Functionally substituted alkylazoles have recently been shown to be highly reactive towards nitrogen electrophiles.[1] This activity was recently used for the synthesis of a variety of azolylpyridazines.[2] In conjunction with our interest in substituted alkylazoles towards electrophiles,[3] we report the results of an investigation towards phenyl isothiocyanate, aryldiazonium chloride and acrylonitrile. In addition, results of our trials to condense α-chloroacetylacetone with azoles **1a**,**b** that results in a novel route to arylazoles are also reported.

RESULT AND DISCUSSION

Reaction of imidazole **1a** and 1,2,4-triazole **1b** with phenacyl bromide yields the respective azolylacetophenones **1c**,**d**.



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a, X = CH ; R = H

b, X = N ; R = H

c, X = CH ; R = CH_2COPh

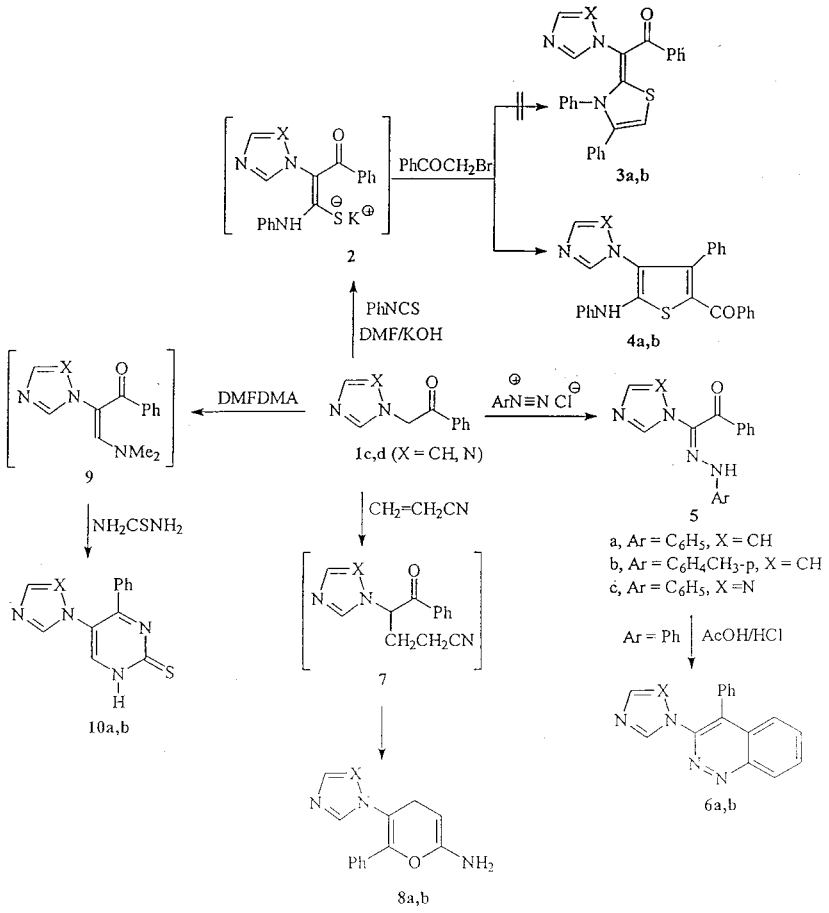
d, X = N ; R = CH_2COPh

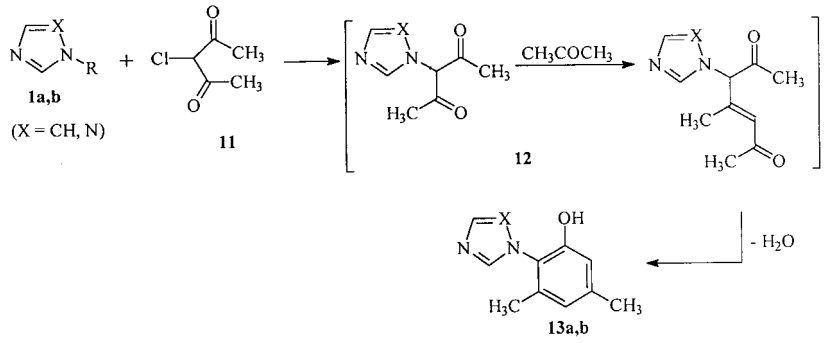
Azolylacetophenones **1c**,**d** reacted with phenyl isothiocyanate to afford in situ an adduct that could not be isolated in pure form. However, when treated with phenacyl bromide in solution, a product to be formulated as **3a**,**b** or isomeric **4a**,**b**, both can be formed from intermediate **2**. Structure **3** was readily ruled-out on the basis of IR and ^{1}H NMR spectra, both of which revealed the presence of an NH, which is concordant with structure **4**.

Compounds **1c**,**d** also coupled with aromatic diazonium salts yielding the corresponding arylhydrazones **5a**–**c**. Boiling of **5a**,**c** in a mixture of acetic and hydrochloric acid yielded 3-azolylcinnolines **6a**,**b**. However, trials to utilize these arylhydrazones as synthetic equivalent to nitrilimines in a way similar to that recently reported by Abdel-Khalik and Elnagdi[4] for alkylpyrimidinium bromide failed. When compounds **1c**,**d** was allowed to react with acrylonitrile in pyridine–water

mixture, a product with *m*/*z* 240 was obtained which does not show CN absorption band in its IR spectra. This means that cyanoethylation took place giving intermediate **7**, which on cycloaddition gave 3-azolylpyrans **8a**,**b**.

Taking in consideration our interest in synthesizing some new bioactive pyrimidines,[5] it was found that reaction of azolylacetophenones **1c**,**d** with dimethylformamide dimethylacetal (DMFDMA) in xylene solution followed by treatment with thiourea yielded 5-azolylpyrimidinethiones **10a**,**b**. It is believed that DMFDMA condenses firstly with azoles **1c**,**d** yielding **9**, which reacted further with thiourea.





In a trial to condense imidazole **1a** and 1,2,4-triazole **1b** with α-chloroacetylacetone **11** in acetone solution and in presence of a base, a product of such condensation was formed but react directly in situ with acetone used as solvent yielding the corresponding arylazoles **13a**,**b**. The formation of arylazoles **13a**,**b** occurred most likely via condensation of acetone molecule with initially formed **12**. To our knowledge this is first reported synthesis of azolylphenols via such a route. This reaction is now being further investigation and the scope of this latter explored.

EXPERIMENTAL

All melting points are uncorrected. The IR spectra were recorded as KBr disks using a FTIR unit Bruker-Vector 22 spectrophotometer. The ^{1}H NMR spectra were recorded on a Bruker Ac-80 spectrometer with [D_6] DMSO as solvent and TMS as internal standard; chemical shifts are reported in δ units (ppm). Mass spectra were measured on a MS-5988 HP model. Microanalyses were performed at microanalytical center, Cairo university.

ω-(Imidazol-1-yl)acetophenone (1c)

A mixture of **1a** (0.01 mol) in acetone (20 mL) was treated with phenacyl bromide (0.012 mol) and triethylamine (0.01 mol) and refluxed for 3 h. The solid product, so formed, was collected by filtration and crystallized from ethanol to give **1c** as a colorless crystals, m.p. 187–188°C; yield (76%). IR (KBr): $\nu = 3340$ (NH), 2980 (aliphatic

CH), 1690 (CO), cm^{-1}.^{1}H NMR $\delta = 5.5$ (s, 2H, $COCH_2$), 6.9–7.6 (m, 8H, Ar-H). MS (EI, 70 eV): $m/z = 186$ [M^+]. Analysis for $C_{11}H_{10}N_2O$ (186): Calcd: C 70.96, H 5.37, N 15.05; Found: C 71.00, H 5.50, N 14.90.

ω-(1,2,4-Triazol-1-yl)acetophenone (1d)

The titled compound was prepared by the method reported in our previous work.[3]

1-(2-Benzoyl-3-phenyl-5-phenylaminothien-4-yl)azoles (4a,b)

To a stirred mixture of **1c** or **1d** (0.025 mol) and potassium hydroxide (0.025 mol) in dimethyl formamide (20 mL), phenyl isothiocyanate (0.025 mol) was added and the reaction mixture was stirred at room temperature for 4 h. Phenacyl bromide (0.025 mol) was added to the above mixture and stirred for 24 h, then poured into cold water and neutralized with 2 M hydrochloric acid. The solid obtained was filtered off and crystallized from ethanol–water (1:1) to give **4** as yellow crystals.

1-(2-Benzoyl-3-phenyl-5-phenylamino-4-thienyl)imidazole (4a): M.p. 208–209°C; yield (87%). IR (KBr): $\nu = 3400$ (NH), 1680 (CO), cm^{-1}. ^{1}H NMR $\delta = 10.8$ (s, 1H, NH), 6.9–7.7 (m, 18H, Ar-H). MS (EI, 70 eV): $m/z = 421$ (M^+), 365 (18.9%), 311 (68%), 105 (100%), 77 (75%).

1-(2-Benzoyl-3-phenyl-5-phenylamino-4-thienyl)-1,2,4-triazole (4b): M.p. 190–192°C; yield (86%). IR (KBr): $\nu = 3290$ (NH), 1681 (CO), cm^{-1}. ^{1}H NMR $\delta = 11.0$ (s, 1H, NH), 6.8–7.6 (m, 15H, Ar-H), 8.8, 8.4 (2s, 2H, triazolyl H-3 and H-5). MS (EI, 70 eV): $m/z = 422$ (M^+, 3.9%), 396 (16.3%), 380 (66.6%), 303 (18.9%), 145 (15.5%), 77 (100%). Analysis for $C_{22}H_{18}N_4SO$ (422): Calcd: C 71.09, H 4.26, N 13.27; Found: C 71.00, H 4.40, N 13.30.

General Procedure for the Preparation of Arylhydrazones 5a–c

Compound **1c** or **1d** (0.01 mol) was dissolved in ethanol (30 mL) and treated with sodium acetate (3.0 g), then gradually treated under stirring with a solution of aryldiazonium chloride (prepared from the corresponding aromatic amine (0.01 mol) and the appropriate quantities of both hydrochloric acid and sodium nitrite). The solid obtained was

filtered off and crystallized from the proper solvent to give **5a**–**c** as yellow crystals.

ω-(Imidazol-1-yl)-ω-phenylhydrazonoacetophenone (5a): M.p. 196–198°C; yield (75%). IR (KBr): $\nu = 3380$ (NH), 2950 (aliphatic CH), 1690 (CO), cm^{-1}. ^1H NMR $\delta = 10.6$ (s, 1H, NH), 6.9–7.4 (m, 13H, Ar-H). MS (EI, 70 eV): $m/z = 290$ (M^+, 21%), 273 (17%), 213 (26%), 77 (100%). Analysis for $C_{17}H_{14}N_4O$ (290): Calcd: C 70.34, H 4.80, N 19.31; Found: C 70.50, H 5.00, N 19.20.

ω-(Imidazol-1-yl)-ω-tolylhydrazonoacetophenone (5b): M.p. 210–212°C; yield (72%). IR (KBr): $\nu = 3390$ (NH), 2930 (aliphatic CH), 1695 (CO), cm^{-1}. ^1H NMR $\delta = 10.8$ (s, 1H, NH), 6.8–7.6 (m, 12H, Ar-H), 2.6 (s, 1H, CH_3). MS (EI, 70 eV): $m/z = 304$ (M^+, 4.9%), 287 (15.3%), 226 (34%), 77 (86%). Analysis for $C_{18}H_{16}N_4O$ (304): Calcd. C 71.05, H 5.20, N 18.42; Found: C 71.30, H 5.40, N 18.50.

ω-(1,2,4-Triazol-1-yl)-ω-phenylhydrazonoacetophenone (5c): The titled compound has been prepared in our previous work.[3]

3-(1-Azolyl)-4-phenylcinnolines 6a,b

Compound **5a** or **5c** (0.01 mol) was dissolved in a mixture of conc. hydrochloric and glacial acid (1:1) and refluxed for 3 h, cooled and poured into cold water. The solid obtained was filtered off and crystallized from the proper solvent to give **5a**–**c** as colorless crystals.

3-(Imidazo-1-yl)-4-phenylcinnoline (6a): M.p. 245–246°C; yield (66%). IR (KBr): $\nu = 3030$ (CH), 1640 (C=N), cm^{-1}. ^1H NMR $\delta = 7$–7.8 (m, 12H, Ar-H). MS (EI, 70 eV): $m/z = 249$ (M^+, 12.5%), 221 (2.78%), 194 (3.76%), 105 (100%), 77 (8.14%).

4-Phenyl-3-(triazo-1-yl)-cinnoline (6b): M.p. 210–212°C; yield (56%). IR (KBr): $\nu = 3030$ (CH), 1645 (C=N), cm^{-1}. ^1H NMR $\delta = 6.9$–7.6 (m, 9H, Ar-H), 8.1 and 8.4 (2s, 2H, triazolyl H3 and H5). MS (EI, 70 eV): $m/z = 273$ (M^+, 1.2%), 220 (15.6%), 222 (3.69%), 106 (100%), 77 (57%). Analysis for $C_{16}H_{11}N_5$ (273): Calcd. C 70.32, H 4.02, N 25.64; Found: C 70.50, H 4.00, N 25.80.

2-Amino-5-(azol-1-yl)-6-phenyl-4H-pyran 8a,b

A mixture of **1c** or **1d** (0.01 mol) and acrylonitrile (0.015 mol) in pyridine (10 mL) and water (3 mL) was refluxed for 6 h, cooled and poured into cold water and neutralize with 2 N hydrochloric acid. The

solid, so formed, was collected and crystallized from DMF-water to give **8a**,**b** as yellow crystals.

2-Amino-5-(imidazol-1-yl)-6-phenyl-4H-pyran (8a): M.p. 286–287°C; yield (89%). IR (KBr): $\nu = 3420$–3330 (NH), 2920 (CH), 1645 (C=N), 1100 (C-O-C) cm^{-1}. ^1H NMR $\delta = 5.5$ (br s, 2H, NH_2), 6.5 (m, 2H, C4-H-pyran), 6.9–7.6 (m, 9H, Ar-H). MS (EI, 70 eV): $m/z = 239$ (M^+, 12.0%), 235 (27.1%), 186 (18.6%), 123 (7.6%).

2-Amino-6-phenyl-5-(triazol-1-yl)-4H-pyran (8b): M.p. > 300°C; yield (65%). IR (KBr): $\nu = 3420$, 3330 (NH_2), 2950 (CH), 1640 (C=N), 1150 (C-O-C) cm^{-1}. ^1H NMR $\delta = 5.6$ (br, 2H, NH_2), 6.5 (m, 2H, C4-H-pyran), 6.9–7.6 (m, 5H, Ar-H), 8.1 and 8.45 (2s, 2H, triazolyl H3 and H5). MS (EI, 70 eV): $m/z = 240$ (M^+, 16%), 236 (33.6%), 185 (21.4%), 152 (28.38%). Analysis for $C_{13}H_{12}N_4O$ (240): Calcd: C 65.00, H 5.00, N 23.33; Found: C 65.40, H 5.20, N 23.50.

5-(Azol-1-yl)-4-phenyl 2(1H)-pyrimidinethiones 10a,b

A mixture of **1c** or **1b** (0.01 mol) and DMFDMA (0.03 mol) in xylene (20 mL) was refluxed for 12 h, then evaporated the excess solvent. To the above reaction mixture thiourea (0.012 mol) was added and refluxed for 1 h, then treated with ethanol and poured into cold water. The solid obtained was filtered off and crystallized from the proper solvent to give **10a**,**b** as yellow crystals.

5-(Imidazol-1-yl)-4-phenyl 2(1H)-pyrimidinethione (10a): M.p. 196–198°C; yield (72%). IR (KBr): $\nu = 3330$ (NH), 1660 (C=N) cm^{-1}. ^1H NMR $\delta = 9.6$ (s, 1H, NH), 6.8–7.6 (m, 9H, Ar-H). MS (EI, 70 eV): $m/z = 254$ (M^+, 6.1%), 187 (21.2%), 77 (100%). Analysis for $C_{13}H_{10}N_4S$ (254): Calcd: C 63.73, H 3.93, N 22.04; Found: C 63.80, H 4.00, N 22.00.

4-Phenyl-5-(1,2,4-triazol-1-yl)-2(1H)-pyrimidinethione (10b): M.p. 150–152°C; yield (78%). IR (KBr): $\nu = 3340$ (NH), 1680 (C=N) cm^{-1}. ^1H NMR $\delta = 9.8$ (s, 1H, NH), 6.9–7.6 (m, 6H, Ar-H), 8.08 and 8.49 (2s, 2H, triazolyl H3 and H5). MS (EI, 70 eV): $m/z = 255$ (M^+, 26%), 198 (12%), 123 (68%), 77 (17%). Analysis for $C_{13}H_{10}N_4S$ (254): Calcd: C 56.47, H 3.52, N 27.45; Found: C 56.40, H 3.50, N 27.60.

1-(3,5-Dimethylphenol-2-yl)azoles 12a,b

A mixture of **1a** or **1c** (0.01 mol) and α-chloroacetylacetone (0.012 mol) in acetone (30 mL) was refluxed for 3 h. The solid obtained

during heating was filtered off and washed with ice-cold ethanol to give **12a**,**b** as colorless crystals.

1-(3,5-Dimethylphenol-2-yl)imidazole (12a): M.p. 235–237°C; yield (86%). IR (KBr): $\nu = 3450$ (OH), 1690 (C=O), 1665 (C=N) cm^{-1}. ^1H NMR $\delta = 9.32$ (s, 1H, OH), 6.8–7.4 (m, 5H, Ar-H), 2.8 (s, 3H, C3-CH_3), 2.6 (s, 3H, C5-CH_3). MS (EI, 70 eV): $m/z = 188$ (M^+, 1.6%), 149 (3.6%), 123 (12%), 84 (100%).

1-(3,5-Dimethylphenol-2-yl)1,2,4-triazole (12b): M.p. 245–247°C; yield (78%). IR (KBr): $\nu = 3440$ (OH), 1690 (C=O), 1660 (C=N) cm^{-1}. ^1H NMR $\delta = 9.3$ (s, 1H, OH), 6.6–7.2 (m, 4H, Ar-H), 8.1 and 8.39 (2s, 2H, triazolyl H-3 and H-5), 3.0 (s, 3H, C3-CH_3), 2.5 (s, 3H, C5-CH_3). MS (EI, 70 eV): $m/z = 189$ (M^+, 2.0%), 167 (15.3%), 129 (22.8%), 84 (100%). Analysis for $C_{10}H_{11}N_3O$ (189): Calcd: C 63.49, H 5.82, N 22.22; Found: C 64.00, H 5.60, N 22.30.

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