FACILE SYNTHESIS OF 3-(THIOPHENOXY/PHENOXY)-4-PHENYL-1,2-DIHYDRO-2-QUINOLINONES

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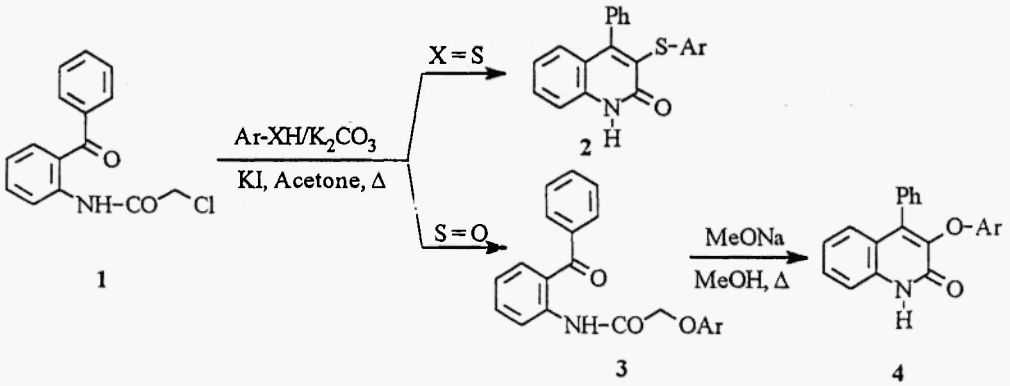
Abstract : 3-(Thiphenoxy/phenoxy)-4-phenyl-1,2-dihydro-2-quinolinones are synthesized in high yields for the first time by the cyclocondensation of N-(2-chloroacetylamino)benzophenone with thiophenol/phenol under basic conditions.

Introduction

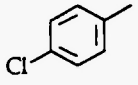
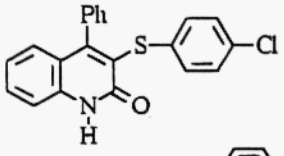
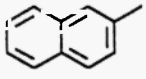
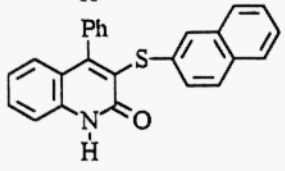
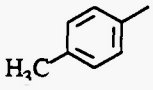
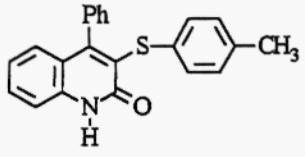
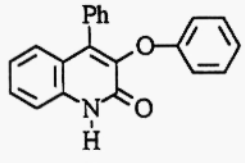
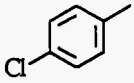
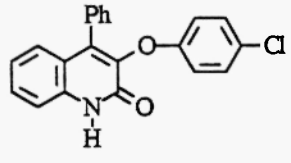
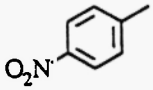
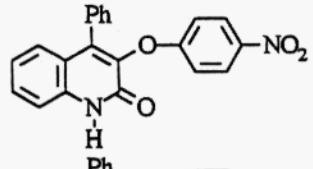
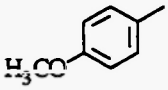
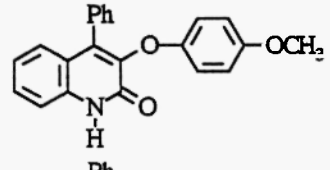
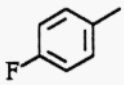
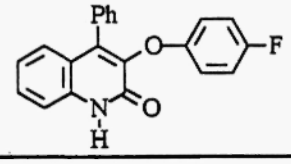
The quinolinone derivatives[1] are current interest in view of the broad spectrum of biological activity exhibited by these compounds as drugs. A few derivatives of quinolinone reported to possess wide variety of pharmacological activity such as antibiotic[2] and antibactirial. The presence of quinolinone moiety in norfloxacin and ciprofloxacin prompted us to develop synthetic routes leading to 3-(thiophenoxy/phenoxy)-4-phenyl-1,2-dihydro-2-quinolinones in order that a series of such compounds could be made for the screening of their antibacterial properties. The effect of substituents at the 3-position of quinolinone is quite remarkable in enhancing the invivo activity.[3]

In this communication, we wish to report a first synthesis of 3-(thiophenoxy /phenoxy)-4-phenyl-1,2-dihydro-2-quinolinones from easily available 2-aminobenzo phenone using basic conditions[4] as shown in the scheme.



Scheme

Table

Entry	Ar	Product	Reaction time / hrs.	M.P. (°C)	Yield (%)
a.			4	236-237	87
b.			4	257-258	84
c.			5	228-229	86
d.			6	241-242	85
e.			6	267-268	87
f.			4	82-83	90
g.			6	221-222	85
h.			4	241-242	80

Results and Discussion

The reaction of N-(2-chloroacetylamino)benzophenone with thiophenols in the presence of anhydrous K_2CO_3, KI and acetone under reflux afforded 3-thio phenoxy-4-phenyl-1,2-dihydro-2-quinolinones in one step. In case of the reaction of N-(2-chloroacetylamino)benzophenone with phenols under above conditions gives 2-(N-aryloxyacetylamino)benzophenones which subsequently cyclise to 3-(phenoxy-4-phenyl-1,2-dihydro-2-quinolinones in the presence of NaOMe in methanol under refluxing conditions.

It is noteworthy to observe that when thiophenols were allowed to react with (1), the expected 2-(N-thiophenoxyacetylamino)benzophenones were not isolated, instead the reaction proceeded on to the next step and directly yielded cyclised products 3-thiophenoxy-4-phenyl-1,2-dihydro-2-quinolinones. This can be rationalised since the sulphur atom renders the hydrogens of the adjacent group highly acidic, a carbanion is formed readily in the presence of base thus resulting in quinolinone ring formation.

In summary, we have developed a facile procedure for the synthesis of a novel series of 3-(thiophenoxy/phenoxy)-4-phenyl-1,2-dihydro-2-quinolinones in 80-90% yields for the first time using a base. The evalution of their biological activity is being investigated and unravelled.

Experimental Section

Melting points were determined on a Buchi Capillary melting point apparatus. The ^{1}H NMR spectra were recorded with TMS as an internal standard in DMSO-d_6 by a Varian Gemin 2000 MHz spectometer, Mass spectra were recorded on a VG 7070H mass spectrometer at 70 eV.

General procedure for the preparation of 3-thiophenoxy-4-phenyl-1,2-dihydro-2-quinolinones (2a-c) : A mixture of substituted thiophenol (5 mmol), 2-chloroacetylaminobenzophenone (5 mmol), potassium carbonate (8 mmol) and potassium iodide (0.15 g) in acetone (15 mL) was refluxed for 4-5 hrs. After complete converion as monitored by TLC, The solvent was removed under *vaccuo* and water (10 ml) was added. The pure product obtained was filtered, washed with water and recrystalized from ethanol.

General procedure for the preparation of 3-phenoxy-4-phenyl-1,2-dihydro-2-quinolinones (4d-h) : To 2-aryloxyacetamidobenzophenol (3d-h) (3 mmol) in methanol (5 ml), was added a freshly prepared solution of sodium methoxide (5 mmol) in methanol (5 mL) while stirring. The

reaction mixture was refluxed for 4-6 hrs. After completion conversion as indicated by TLC, the solvent was removed under *vaccuo* and water (10 ml) was added to the residue. The product obtained as a solid was collected by filtration, washed with water and recrystalized from ethanol.

2a) 3-(4'-chlorothiophenoxy)-4-phenyl-1,2-dihydro-2-quinolinone : ^{1}H NMR (DMSO-d_6) : δ 7.1 (m, 8H), 7.4 (m, 5H), 12.1 (brs, 1H). Mas (70 eV) m/e (rel. intensity) : 363 (M^+, 100), 234 (6), 165 (5). 63 (20). Anal. Calcd. For $C_{21}H_{14}NOSCl$ H, 3.89; C, 69.41; N, 3.86; Cl, 9.63. Found : H, 3.75; C, 69.32; N, 3.72; Cl, 9.49.

2b) 3-(4'-Naphthylthiophenoxy)-4-phenyl-1,2-dihydro-2-quinolinone : ^{1}H NMR (DMSO-d_6) : δ 7.5 (m, 16H), 12.1 (brs, 1H). Mass (70 eV) m/e (rel. intensity) : 379 (M^+, 8), 318 (80), 159 (70), 115 (100), 69 (45). Anal. Calcd. For $C_{25}H_{17}NOS$: H, 4.52; C, 79.13; N, 3.69. Found : H, 4.38; C, 79.02; N, 3.58.

2c) 3-(4'-Methylthiophenoxy)-4-phenyl-1,2-dihydro-2-quinolinone : ^{1}H NMR (DMSO-d_6) : δ 2.3 (s, 3H), 6.8 (s, 4H), 7.0 (brs, 2H), 7.2 (m, 2H), 7.4 (m, 5H), 12.0 (brs, 1H). Mass (70 eV) m/e (rel. intensity) : 343 (M^+, 5), 246 (7), 83 (100). Anal. Calcd. For $C_{22}H_{17}NOS$: H, 4.99, C, 76.94; N, 4.08; Found H, 4.85; C, 76.78; N, 3.88.

4d) 3-Phenoxy-4-phenyl-1,2-dihydro-2-quinolinone : ^{1}H NMR (DMSO-d_6) : δ 6.8 (d, J = 8.6, Hz, 2H), 7.3 (m, 12H), 12.2 (brs, 1H). Mass (70 eV) m/e (rel. intensity) : 313 (M^+, 30), 312 (35), 196 (100), 105 (20), 77 (30). Anal. Calcd. For $C_{21}H_{15}NO_2$: H, 4.83; C, 80.48; N, 4.47. Found : H, 4.72; C, 80.27; N, 4.32.

4e) 3-(4'-chlorophenoxy)-4-phenyl-1,2-dihydro-2-quinolinone : ^{1}H NMR (DMSO-d_6) δ 6.8 (d, J = 8.6 Hz, 2H), 7.2 (m, 4H), 7.3 (m, 2H), 7.5 (m, 5H), 12.2 (brs, 1H). Mass (70 eV) m/e (rel. intensity) : 347 (M^+, 100), 196 (80), 120 (40), 77 (50). Anal. Calcd. For $C_{21}H_{14}NO_2Cl$: H, 4.07; C, 72.61; N, 4.03; Cl, 10.08. Found : H, 3.86; C, 72.56; N, 3.91; Cl, 10.02.

4f) 3-(4'-Nitrophenoxy)-4-phenyl-1,2-dihydro-2-quinolinone : ^{1}H NMR (DMSO-d_6) δ 7.5 (m, 11H), 8.2 (d, J = 8.6 Hz, 2H), 9.7 (brs, 1H). Mass (70 eV) m/e (rel. intensity) : 358 (M^+, 5), 244 (100), 196 (20), 105 (80), 77 (80). Anal. Calcd. For $C_{21}H_{14}N_2O_4$: H, 3.94; C, 70.63; N, 7.82. Found : H, 3.86; C, 70.49; N, 7.68.

4g) 3-(4'-Methoxyphenoxy)-4-phenyl-1,2-dihydro-2-quinolinone : ^{1}H NMR (DMSO-d_6) : δ 3.7 (s, 1H), 6.6 (s, 4H), 7.2 (m, 9H), 12.0 (brs, 1H). Mass (70 eV) m/e (rel. intensity) : 343 (M^+, 100), 196 (18), 180 (20), 105 (20), 77 (30). Anal. Calcd. For $C_{22}H_{17}NO_3$: H, 4.99; C, 76.94; N, 4.8. Found : H, 4.78; C, 76.83; N, 3.87.

4h) 3-(4'-Fluorophenoxy)-4-phenyl-1,2-dihydro-2-quinolinone : ^{1}H NMR (DMSO-d_6) : δ 7.2 (m, 13H), 11.8 (brs, 1H). Mass (70 eV) m/e (rel. intensity) : 331 (M^+, 100), 208 (15), 180 (20), 95 (15), 77 (20). Anal. Calcd. For $C_{21}H_{14}NO_2F$: H, 4.26; C, 76.12; N, 4.23. Found : H, 4.14; C, 76.03; N, 3.98.

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Refereces :

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