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Synthesis of phthalimido or succinimido[2-aryl-4-oxo-3-{2-phenyl-4(3*H*)-quinazolinon-3-yl}-1,3-thiazolidin-5-yl]ethanoate

Shweta Sharma, Chirag Sharma, Bhawana Thadhaney and G. L. Talesara*

Synthetic Organic Chemistry Laboratory, Department of Chemistry, M. L. Sukhadia University, Udaipur-313 001, Rajasthan, India

E-mail : gtalesara@yahoo.com

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Abstract : Treatment of benzoxazine 1 with hydrazine hydrate in ethanol furnished 3-amino-2-phenylquinazolin-4-(3*H*)-one 2, which upon condensation with aldehydes 3a-d yielded the corresponding 3-arylideneamino derivatives 4a-d. Cyclization of these derivatives using mercaptosuccinic acid afforded 1,3-thiazolidin-4-one ethanoic acids 5a-d, which after esterification with *N*-hydroxyphthalimide or *N*-hydroxysuccinimide via acid chlorides produced the respective ethanoic esters 7a-e.

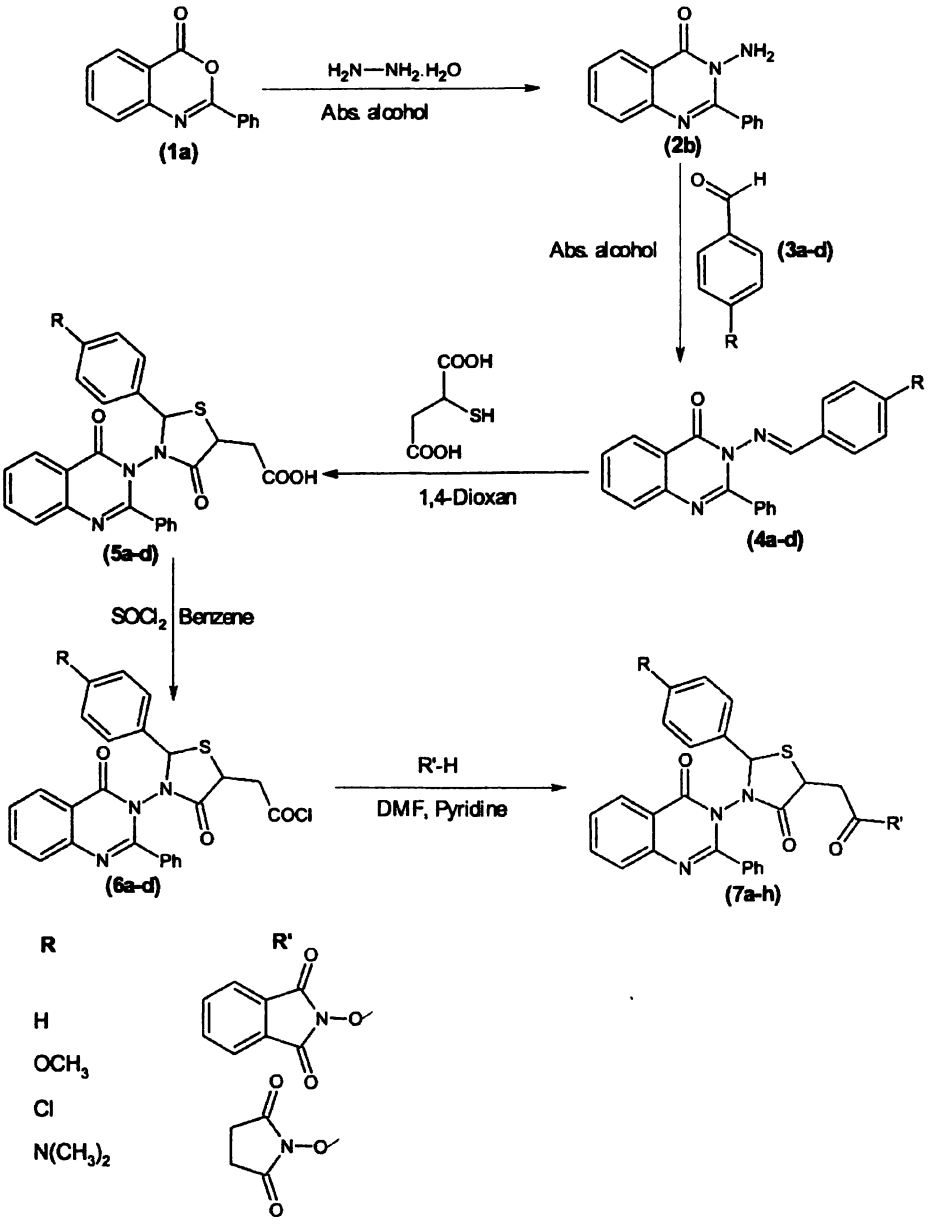
Keywords : *N*-Hydroxyphthalimide, *N*-hydroxysuccinimide, benzoxazine, quinazolinone, thiazolidin.

Introduction

Quinazolinones derivatives are widely used in agrochemicals as plant virucides[1], antifungal agents[2] and herbicides[3]. Molecules based on quinazoline and quinazolinone exhibit a multitude of interesting pharmacological activities like antimicrobial[4], anti-HIV[5], antitubercular[6], anticancer[7], anticonvulsant[8], antidepressant[9], hypolipidemic[10], antiulcer[11] and immunotropic activities[12]. These are also known to act as thymidylate synthase[13], poly(ADP-ribose) polymerase (PARP)[14] and protein tyrosine kinase[15] inhibitors. It was found that the incorporation of the 3-arylideneamino substituent enhanced the antibacterial activity of the quinazolone system[16]. On the other hand, heterocycles containing the thiazolidinone nucleus also exhibit various pharmacological activities like antioxidant[17], antifungal[18], hypnotic[19], retinoidal[20], antipsychotic[21], anticonvulsant[22] and many more. Imidoxy compounds (viz. phthalimidoxy and succinimidoxy) were reported to possess promising pharmacological properties. The most promising imidoxy anticonvulsant was ethyl phthalimidoxy acetate[23] and that plays an important role in the peptide synthesis and inhibition of human leukocyte elastase[24]. Because of these established biological activities we became interested in the synthesis of a series of phthalimido and succinimido derivatives of [2-aryl-4-oxo-3-{2-phenyl-4(3*H*)-quinazolinone-3-yl}-1,3-thiazolidin-5-yl]ethanoic acid with the aim of obtaining enhanced biological activity.

Results and discussion

The strategy to synthesize the target compounds **7a-h** is shown in the Scheme 1. The starting 2-phenyl-3,1-benzoxazin-4(3*H*)-one **1** was prepared by reported method[25]. Benzoxazine **1** was converted to 3-amino-2-phenylquinazolin-4(3*H*)-one **2** by its nucleophilic substitution reaction with hydrazine hydrate. Insertion of nitrogen in the ring was characterized by disappearance of band at 1180 cm^{-1} of C–O and shift of carbonyl band from 1720 to 1702 cm^{-1}. Appearance of new peaks near 3400 and 3300 cm^{-1} for N–H stretching also helped in assigning structure of **2**. To prepare Schiff bases **4a-d**, the compound **2** was treated with various aromatic aldehydes **3a-d** in presence of catalytic amount of acetic acid in absolute ethanol. The IR spectrum of **4a** exhibit absorption band at 1632 cm^{-1} due to -C=N stretching frequency. Cyclocondensation of **4a-d** with mercaptosuccinic acid in the presence of few drops of zinc chloride furnished thiazolidinone derivatives **5a-d**. IR spectra of compounds **5a-d** show characteristic absorption bands at 3427–2999 br. and 1687–1679 cm^{-1} which are due to O–H and C=O (cyclic) groups respectively. The ^1H NMR spectra of these compounds exhibited singlet for -OH group at δ 10.40–10.30 and doublet of CH_2 at δ 3.22–3.15, which indicate the presence of CH-COOH group at 5th position of thiazolidinone ring. Compounds **6a-d** were obtained in good yield by refluxing the compounds **5a-d** with thionyl chloride in benzene to give ethanoyl chloride derivatives



Scheme 1

6a-d. The appearance of C-Cl peak at 749 cm^{-1} and disappearance of broad peak of -OH at 3427-3112 cm^{-1} indicate the formation of C-Cl bond. Subsequently the chlorine atom in CH_2-CO-Cl was replaced by the phthalimidoxy or succinimidoxy group to give the title compounds **7a-h**. The IR, ^1H NMR and Mass spectra of the final compounds **7a-h** supported the proposed structure. The ^1H NMR shows triplet at δ 4.7 and doublet at δ 3.4 confirmed the presence of CH-CH_2-CO groups. Furthermore, stretching of CO-N-CO at 1688-1669 cm^{-1} confirmed the presence of imidoxy moiety in the structure of synthesized compounds. Molecular ion peak appearing in the mass spectra also support the structure of final compounds **7a-h**.

Experimental

General procedures : Melting points were taken in open capillary tubes and are therefore uncorrected. Pu-

rity of the compounds was checked on silica gel G TLC plates of 2 mm thickness using *n*-hexane and ethyl acetate as solvent system. The visualization of spot was carried out in an iodine chamber. The IR spectra were recorded on Perkin-Elmer spectrometer. The ^1H NMR and ^{13}C NMR spectra were scanned on a Bruker DRX-300 MHz spectrometer (300 MHz) in $CDCl_3$ or DMSO-d_6 using TMS as internal standard and chemical shifts are expressed in δ ppm. The mass spectra were recorded on a Jeol SX-102 (FAB) spectrometer.

Synthesis of 3-amino-2-phenylquinazolin-4(3H)-one **2** :

Compound (**1**, 0.01 mol) was dissolved in ethanol and hydrazine hydrate (0.015 mol) was added to it with a catalytic amount of pyridine. Reaction mixture was refluxed for 4 h and after cooling a crystalline product was obtained. It was filtered and recrystallized from ethanol to yield needle shaped shining white crystals.

2 : Yield 70%, m.p. 165 °C; IR (KBr) : 3418, 3340, 3010, 1702, 1585 cm^{-1}; ^1H NMR (DMSO-d_6) : δ 7.32–7.12, 2.56 (Found : N, 17.68. Calcd. for $C_{14}H_{13}N_3O$: N, 17.71%).

Synthesis of 3-benzylideneamino-2-phenylquinazolin-4(3H)-one **4a** :

An equimolar mixture of 3-amino-2-phenylquinazolin-4(3*H*)-one (**2**, 0.01 mol) and benzaldehyde (**3a**, 0.01 mol) in ethanol containing acetic acid was refluxed for 6 h. Excess solvent was distilled off and the residue was cooled. The solid thus separated was filtered, washed and recrystallized from ethanol.

4a : Yield 78%, m.p. 140 °C; IR (KBr) : 3069, 1719, 1632, 1481 cm^{-1}; ^1H NMR ($CDCl_3$) : δ 6.10, 7.99–7.56 (Found : N, 12.86. Calcd. for $C_{21}H_{15}N_3O$: N, 12.91%).

Similarly, compounds **4b-d** were prepared with some change in reflux time and reaction work up. Their characteristic spectral and analytical data are given below :

4b : Yield 69%, m.p. 200 °C; IR (KBr) : 3075, 1710, 1635, 1485 cm^{-1}; ^1H NMR ($CDCl_3$) : δ 8.01–7.55, 6.25, 2.14 (Found : N, 11.71. Calcd. for $C_{22}H_{17}N_3O_2$: N, 11.82%).

4c : Yield 65%, m.p. 210 °C; IR (KBr) : 3080, 1715, 1638, 1486, 749 cm^{-1}; ^1H NMR ($CDCl_3$) : δ 8.00–7.60, 6.21 (Found : N, 11.61. Calcd. for $C_{21}H_{14}ClN_3O$: N, 11.68%).

4d · Yield 70%, m.p. 219 °C; IR (KBr) : 3072, 1700, 1630, 1481 cm^{-1}; ^1H NMR ($CDCl_3$) : δ 8.10–7.50, 6.15, 2.73 (Found : N, 15.18. Calcd. for $C_{23}H_{20}N_4O$: N, 15.21%).

Synthesis of [2-phenyl-4-oxo-3-{2-phenyl-4(3H)-quinazolinone-3-yl}-1,3-thiazolidin-5-yl]ethanoic acid **5a** :

To a well stirred solution of compound (**4a**, 0.01 mol) in dioxane (50 mL) containing a pinch of anhydrous zinc chloride, was added mercaptosuccinic acid (0.013 mol) and the mixture refluxed for 8 h on a steam bath. The separated solid was filtered and recrystallized from ethanol.

5a : Yield 55%, m.p. 120 °C; IR (KBr) : 3427–3112, 3048, 1704, 1682, 1442, 701 cm^{-1}; ^1H NMR ($CDCl_3$) : δ 10.30, 7.87–7.19, 4.23, 3.60, 3.14 (Found : N, 9.10. Calcd. for $C_{25}H_{19}N_3O_4S$: N, 9.18%).

Likewise, compounds **5b-d** were prepared with some change in reaction conditions. Their characteristic spectral and analytical data are given below :

5b : Yield 60%, m.p. 280 °C; IR (KBr) : 3390–3110, 3050, 1710, 1685, 1448, 695 cm^{-1}; ^1H NMR ($CDCl_3$) : δ 10.39, 7.91–7.24, 4.19, 3.63, 3.19 (Found : N, 8.52. Calcd. for $C_{26}H_{21}N_3O_5S$: N, 8.62%).

5c : Yield 72%, m.p. 106 °C; IR (KBr) : 3410–2999, 3055, 1715, 1687, 1450, 693 cm^{-1}; ^1H NMR ($CDCl_3$) : δ 10.40, 7.84–7.29, 4.19, 3.65, 3.21 (Found : N, 8.48. Calcd. for $C_{25}H_{18}ClN_3O_4S$: N, 8.54%).

5d : Yield 60%, m.p. 257 °C; IR (KBr) : 3399–3108, 3046, 1709, 1679, 1442, 695 cm^{-1}; ^1H NMR ($CDCl_3$) : δ 10.33, 7.89–7.31, 4.15, 3.60, 3.15, 2.75 (Found : N, 11.10. Calcd. for $C_{27}H_{24}N_4O_4S$: N, 11.19%).

Synthesis of [2-phenyl-4-oxo-3-{2-phenyl-4(3H)-quinazolinone-3-yl}-1,3-thiazolidin-5-yl]ethanoyl chloride **6a** :

A solution of **5a** (0.01 mol) in benzene (25 mL) and thionyl chloride (0.02 mol) was refluxed for 1 h on water bath. Excess of thionyl chloride was removed by distillation under reduced pressure. The solid obtained upon cooling was recrystallized from methanol.

6a · Yield 68%, m.p. 200 °C; IR (KBr) : 3058, 1700, 1685, 749, 692 cm^{-1}; ^1H NMR ($CDCl_3$) : δ 7.76–7.23, 4.10, 3.23, 2.96 (Found : N, 8.75. Calcd. for $C_{25}H_{18}ClN_3O_3S$: N, 8.83%).

Likewise, compounds **6b-d** were prepared with some change in reaction conditions. Their characteristic spectral and analytical data are given below :

6b : Yield 65%, m.p. 225 °C; IR (KBr) : 3074, 1726, 1688, 745, 695 cm^{-1}; ^1H NMR ($CDCl_3$) : δ 7.81–7.19,

4.14, 3.26, 2.90 (Found : N, 8.25. Calcd. for $C_{26}H_{20}ClN_3O_4S$: N, 8.30%).

6c : Yield 62%, m.p. 160 °C; IR (KBr) : 3055, 1715, 1691, 750, 690 cm^{-1}; ^1H NMR ($CDCl_3$) : δ 7.84–7.25, 4.16, 3.20, 2.98 (Found : N, 8.15. Calcd. for $C_{25}H_{17}Cl_2N_3O_3S$: N, 8.23%).

6d : Yield 65%, m.p. 250 °C; IR (KBr) : 3071, 1704, 1677, 695, 751 cm^{-1}; ^1H NMR ($CDCl_3$) : δ 7.72–7.21, 4.19, 3.18, 2.98, 2.77 (Found : N, 10.70. Calcd. for $C_{25}H_{19}ClN_3O_4S_2$: N, 10.79%).

Synthesis of phthalimido[2-phenyl-4-oxo-3-{2-phenyl-4(3H)-quinazolinone-3-yl}-1,3-thiazolidin-5-yl]ethanoate **7a** :

N-Hydroxyphthalimide (0.01 mol) was added to a well-stirred solution of **7a** (0.01 mol) in dry DMF (30 mL) containing pyridine (0.02 mol) as a base. The reaction mixture was refluxed for 7 h, filtered and the filtrate was poured on crushed ice. The precipitated solid was collected and crystallized from ethanol.

7a : Yield 65%, m.p. 160 °C; IR (KBr) : 3069, 2818, 1704, 1672, 1206, 801, 696, 1388, 952 cm^{-1}; ^1H NMR ($CDCl_3$) : δ 7.91–7.55, 4.00, 3.62, 3.01; ^{13}C NMR (DMSO-d_6) : δ 169.1, 167.2, 152.9, 40.5, 33.8; MS : *m/z* 602 $[M]^{+\bullet}$, 470, 456, 398, 367, 221, 204, 190, 162, 146, 132 (Found : N, 9.21. Calcd. for $C_{33}H_{22}N_4O_6S$: N, 9.30%).

Likewise, compounds **7b-h** were prepared with some change in reaction conditions. Their characteristic spectral and analytical data are given below :

7b : Yield 74%, m.p. 240 °C; IR (KBr) : 3030, 1722, 1688, 1170, 1215, 820, 685, 1390, 940 cm^{-1}; ^1H NMR ($CDCl_3$) : δ 7.86–7.51, 4.12, 3.63, 3.11, 2.95; ^{13}C NMR (DMSO-d_6) : δ 169.3, 167.6, 152.4, 45.7, 40.3, 34.3; MS : *m/z* 632 $[M]^{+\bullet}$, 500, 486, 428, 397, 221, 204, 190, 162, 146, 132 (Found : N, 8.79. Calcd. for $C_{34}H_{24}N_4O_7S$: N, 8.86%).

7c : Yield 68%, m.p. 196 °C; IR (KBr) : 3031, 1711, 1687, 1381, 1211, 951, 755, 693 cm^{-1}; ^1H NMR ($CDCl_3$) : δ 7.85–7.69, 4.18, 3.64 2.96; ^{13}C NMR (DMSO-d_6) : δ 170.8, 167.9, 152.6, 134.6, 40.8, 34.7; MS : *m/z* 637 $[M]^{+\bullet}$, 639 $[M+2]^{+\bullet}$, 504, 490, 432, 401, 221, 204, 190, 162, 146, 132 (Found : N, 8.70. Calcd. for $C_{33}H_{21}ClN_4O_6S$: N, 8.79%).

7d : Yield 59%, m.p. 176 °C; IR (KBr) : 3020, 1718, 1682, 1213, 1330, 948, 800, 690 cm^{-1}; ^1H NMR ($CDCl_3$) : δ 7.88–7.60, 4.18, 3.70, 2.95, 2.74 ; ^{13}C NMR (DMSO-d_6) : δ 168.8, 167.8, 152.1, 40.1, 33.6 ; MS : *m/z* 645 $[M]^{+\bullet}$, 513, 499, 441, 410, 221, 204, 190, 162, 146, 132 (Found : N, 10.79. Calcd. for $C_{35}H_{27}N_5O_6S$: N, 10.85%).

7e : Yield 59%, m.p. 235 °C; IR (KBr) : 3045, 1715, 1670, 1227, 1350, 947, 829, 689 cm^{-1}; ^1H NMR ($CDCl_3$) : δ 7.99–7.50, 4.20, 3.67, 3.05, 2.79; ^{13}C NMR (DMSO-d_6) : δ 169.3, 167.5, 152.7, 42.1, 40.6, 33.9; MS : *m/z* 554 $[M]^{+\bullet}$, 470, 456, 440, 398, 221, 156, 142, 114, 98 (Found : N, 10.02. Calcd. for $C_{29}H_{22}N_4O_6S$: N, 10.10%).

7f : Yield 62%, m.p. 240 °C; IR (KBr) : 3081, 1731, 1669, 1355, 952, 836, 694 cm^{-1}; ^1H NMR ($CDCl_3$) : δ 7.85–7.49, 4.20, 3.71, 3.14, 2.77; ^{13}C NMR (DMSO-d_6) : δ 169.5, 167.5, 152.5, 45.4, 42.3, 40.8, 34.4; MS : *m/z* 584 $[M]^{+\bullet}$, 500, 486, 470, 428, 221, 156, 142, 114, 98 (Found : N, 9.58. Calcd. for $C_{30}H_{24}N_4O_7S$: N, 9.50%).

7g : Yield 74%, m.p. 255 °C; IR (KBr) : 3046, 1730, 1688, 1385, 945, 841, 752, 681 cm^{-1}; ^1H NMR ($CDCl_3$) : δ 7.90–7.52, 4.11, 3.70, 3.11, 2.77; ^{13}C NMR (DMSO-d_6) : δ 170.5, 167.8, 152.9, 134.5, 42.9, 40.6, 34.1; MS : *m/z* 589 $[M]^{+\bullet}$, 590 $[M+2]^{+\bullet}$, 504, 490, 474, 432, 221, 156, 142, 114, 98 (Found : N, 9.46. Calcd. for $C_{29}H_{21}ClN_4O_6S$: N, 9.51%).

7h : Yield 59%, m.p. 199 °C; IR (KBr) : 3033, 1726, 1677, 984, 832, 676 cm^{-1}; ^1H NMR ($CDCl_3$) : δ 7.85–7.58, 3.79, 4.09, 3.15, 2.89; ^{13}C NMR (DMSO-d_6) : δ 168.5, 167.9, 152.3, 42.6, 40.5, 33.2; MS : *m/z* 597 $[M]^{+\bullet}$, 513, 499, 483, 441, 221, 156, 142, 114, 98 (Found : N, 10.65. Calcd. for $C_{31}H_{27}N_5O_6S$: N, 10.72%).

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