*Proc. 2nd Saudi Sci. Conf., Fac. Sci., KAU, 15-17 March 2004, **Part III,*** pp 53-59 (2005 A.D./1425 A.H.)

Phase-Transfer Catalyzed Alkylation and Cycloalkylation of 2-Mercaptoquinazolin-4(3H)-One.

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ABSTRACT. Solid/liquid phase-transfer catalyzed alkylation of 2-mercaptoquinazolin-4(3H)-one at 25°C by different organohalogen compounds in the presence of tetra-butylammonium bromide as catalyst underwent, exclusively, S-monoalkylation or S- and N- di- or cycloalkylation depending on the nature of alkylating agents.

Keywords: *Phase-transfer Catalysis (PTC), alkylation, cycloalkylation, mercaptoquinazolinone.*

Introduction

Phase-transfer catalysis (PTC) is one of the promising methods in organic synthesis of specialty chemicals. In the last 20 years, a steadily increasing number of published papers and patents dealing with phase transfer catalysis topics and their applications. PTC is not merely important for substitutional reactions but, nowadays, it is being extensively applied in polymer chemistry, heterocyclic chemistry, organometallic synthesis, agrochemicals, dyes, flavors, perfumes and pharmaceutical manufacture[1-3].

The technique of PTC has, extensively, been applied in the organic synthesis via substitution, displacement, condensation, elimination, Ylide-mediated reactions, redox and polymerization. The most advantages of using PTC technique to synthesize organic chemicals are the enhancement of the reaction rate, carrying out the reaction at moderate conditions, obtaining high selectivity of the main product with high conversion of the reactants [4, 5].

On the other hand, 4(3H)-quinazolinones are the most frequently encountered heterocycles in medicinal chemistry with wide applications including anticonvulsant[6], antihypertensive[7], antidiabetic[8], antibacterial[9], antitumor[10], antihistaminic[11] and antiinflammatory[12] activities. Recent investigations on biological activity of heterocycles containing benzimidazole ring, clearly, show that they play an important role as selective neuropeptide YY1 receptor antagonists[13], factor Xa (FXa) inhibitors[14], 5-lipoxygenase inhibitors for use as novel antiallergic agents[15], poly (ADP-ribose) polymerase (PARP) inhibitors[16] and as human cytomegalovirus (HCMV) inhibitors[17].

Experimental

Melting points reported are uncorrected. IR spectra were recorded on Perkin Elmer's Spectrum RXIFT-IR spectrophotometer (ν in cm^{-1}) using KBr Wafer technique . The NMR spectra were recorded on Bruker Avance DPX400 spectrometer, using TMS as internal standard (chemical shifts in δ values in ppm). Elemental analyses were preformed using Perkine Elmer 2400, Series II micro analyzer. The key starting, 2-mercaptoquinazolin-4(3H)-one (**1**) is an Aldrich product and used without further purification.

General procedure

To a solution of 2-mercaptoquinazolin-4(3H)-one (1.78 g, 0.01 mol), (**1**) in dioxane (50 ml), anhydrous K_2CO_3 (2.7 g, 0.02 mol) and tetrabutylammonium bromide (TBAB) (0.9 g, 0.003 mol), the monohalogen organic reagents (0.03 mol) such as ethyl bromide, allyl bromide, bromoacetylacetone, diethyl bromomalonate, methyl iodide, benzyl bromide, ω-bromo-4-methoxyacetophenone, ethyl bromoacetate and chloroacetyl chloride or dihalgen organic reagent (0.01 mol), such as 1,2-dibromoethane, 1,3-dibromopropane and chloroacetyl chloride was added. The reaction mixture was stirred, vigorously at 25 °C and monitored by TLC over the reaction period. After completion of the reaction, the dioxane was separated by filtration and the solvent was evaporated, then the residue was triturated with Pet. Ether 60-80° to release the excess of unreacted halogen reagent, then the residue was crystallized from the suitable solvent to give the product **2-4**. The K_2CO_3 residue was dissolved in water (50ml) and acidified by hydrochloric acid (15% solution) to confirm if an acidic by-product is existed. In all cases, there is no by-product isolated from K_2CO_3 residue.

2-Mercaptoquinazolin-4(3H)-one (1). ^{1}H NMR: δ (DMSO), 7.27 (t, 1H, Ph-H), 7.39 (d, 1H, Ph-H), 7.63 (t, 1H, Ph-H), 8.02 (d, 1H, Ph-H), 11.97 (s, 1H, NH), 12.56 (s, 1H, SH); ^{13}C NMR: δ (DMSO), 116.00 (C), 126.03 (CH), 127.12 (CH), 134.7 (CH), 135.73 (CH), 140.46 (C), 159.99 (C_2), 174.35 (C_4).

2-(Ethylthio)quinazolin-4(3H)-one (2a). White crystals from ethanol; $C_{10}H_{10}N_2OS$ (206.71), Calcd.: C, 58.23, H, 4.89, N, 13.5; found: C, 58.55, H, 4.82,N, 12.99; yield 64%; m. p. 147 °C; IR, 1580, 1678, 2878, 3318; ^{1}H NMR, δ ($CDCl_3$). 1.47 (t, 3H, CH_3), 3.32 (q, 2H, S-CH_2), 7.40, 7.61, 7.72, 8.26 (4H, Ar-H), 10.90 (s, 1H, NH); ^{13}C NMR, δ ($CDCl_3$), 14.44 (CH_3), 25.25 (CH_2), 119.87 (C), 125.73 (CH), 126.39 (CH), 126.60 (CH), 134.83 (CH), 149.21 (C), 154.54 (C_2), 163.03 (C_4).

2-(Allylthio)quinazolin-4(3H)-one (2b). White crystals from Pet. Ether 60-80°; $C_{11}H_{10}N_2OS$ (218.28), Calcd.: C, 60.53, H, 4.62, N, 12.83; found: C, 60.47, H, 4.58, N, 12.77; yield 58%; m. p. 154 °C; IR, 1581, 1668, 2871, 3310; ^{1}H NMR, δ ($CDCl_3$), 4.41 (d, 2H, CH_2), 5.62 (d, 1H, =CH_b), 5.82 (d, 1H, =CH_a), 6.45 (m, 1H, -CH=), 7.83, 8.03, 8.16, 8.67 (4H, Ar-H), 11.90 (s, 1H, NH); ^{13}C NMR, δ ($CDCl_3$), 33.32 (CH_2), 118.73 (=CH_2), 120.26 (C), 124.92 (CH), 125.73 (CH), 127.55 (CH), 133.87 (CH), 135.47 (CH), 149.01 (C), 154.24 (C_2), 163.03 (C_4).

3-[(4-Oxo-3,4-dihydroquinazolin-2-yl)thio]pentane-2,4-dione (2c). Orange crystals from ethanol; $C_{13}H_{12}N_2O_3S$ (276.32), Calcd.: C, 56.51, H, 4.38, N, 10.14; found: C, 56.46, H, 4.33, N, 10.06; yield 62%; m. p. 208 °C; IR, 1584, 1671, 2868, 3011; ^{1}H NMR, δ ($CDCl_3$), 2.35 (s, 6H, 2xCH_3), 4.11 (s, 1H, CH), 7.41-8.24 (4H, Ar-H), 12.53 (s, 1H, NH);

^{13}C NMR, δ ($CDCl_3$), 26.94 (CH_3), 64.67 (CH), 121.67 (C), 126.34 (CH), 127.18 (CH), 134.79 (CH), 147.27 (C), 154.88 (C_2), 162.07 (C_4), 197.13 (C=O).

Diethyl[(4-oxo-3,4-dihydroquinazolin-2-yl)thio]malonate (2d). Pale yellow crystals from ethanol; $C_{15}H_{16}N_2O_5S$ (336.37), Calcd.: C, 53.56, H, 4.75, N, 8.33; found: C, 53.66, H, 4.65, N, 8.41; yield 66%; m. p. 126 °C; IR, 1658, 1747, 2881, 2982, 3321; ^{1}H NMR, δ ($CDCl_3$), 1.31 (txt, 6H, 2xCH_3), 4.24 (qxq, 4H, 2xOCH_2), 5.62 (s, 1H, C<u>H</u>), 7.36-8.22 (4H, Ar-<u>H</u>), 12.07 (s, 1H, N<u>H</u>); ^{13}C NMR, δ ($CDCl_3$), 51.82 (CH_3), 60.61 (CH), 62.94 (CH_2), 119.81 (C), 126.28 (CH), 126.80 (CH), 135.23 (CH), 148.57 (C), 152.73 (C_2), 163.39 (C_4), 165.60 (C=O).

3-Methyl-2-(methylthio)quinazolin-4(3H)-one (2e). White crystals from Pet. Ether 40-60°; $C_{10}H_{10}N_2OS$ (206.27), Calcd.: C, 58.23, H, 4.89, N, 13.58; found: C, 58.65, H, 4.82, N, 13.69; yield 85%; m. p. 66-68 °C; IR, 1556, 1667, 2934; ^{1}H NMR, δ ($CDCl_3$), 2.65 (s, 3H, S-CH_3), 3.60 (s, 3H, N-CH_3), 7.35, 7.52, 7.65, 8.19 (4H, Ar-<u>H</u>); ^{13}C NMR, δ ($CDCl_3$), 14.45 (S-CH_3), 30.84 (N-CH_3), 118.89 (C), 124.65 (CH), 126.27 (CH), 127.65 (CH), 134.86 (CH), 147.39 (C), 157.48 (C_2), 161.81 (C_4).

3-Benzyl-2-(bezylthio)quinazolin-4(3H)-one (2f). White crystals from Pet. Ether 60-80°; $C_{22}H_{18}N_2OS$ (358.47), Calcd.: C, 73.72, H, 5.06, N, 7.81; found: C, 73.68, H, 5.12, N, 7.89; yield 73%; m. p. 95-97 °C; IR, 1565, 1691, 2938, 3032; ^{1}H NMR, δ ($CDCl_3$), 4.50 (s, 2H, S-CH_2), 5.35 (s, 2H, N-CH_2), 7.23 (m, 10H, 2xC_6H_5), 7.40, 7.57, 7.65, 8.22 (4H, Ar-<u>H</u>); ^{13}C NMR, δ ($CDCl_3$), 37.24 (S-CH_2), 47.77 (N-CH_2), 119.67 (C), 126.48 (CH), 127.88 (CH), 129.06 (CH), 129.80 (CH), 134.93 (CH), 135.94 (C), 136.79 (C), 147.85 (C), 156.84 (C_2), 162.45 (C_4).

3-[2-(4-Methoxyphenyl)-2-oxoethyl]-2-{[2-(4-methoxyphenyl)-2-oxoethyl]thio}quinazolin-4(3H)-one (2g). White crystals from ethanol; $C_{26}H_{22}N_2O_5S$ (474.54), Calcd.: C, 65.81, H, 4.67, N, 5.90; found: C, 65.92, H, 4.59, N, 6.01; yield 54%; m. p. 169 °C; IR, 1597, 1680, 2909; ^{1}H NMR, δ ($CDCl_3$), 3.85 (s, 3H, O-CH_3), 3.97 (s, 3H, O-CH_3), 4.97 (s, 2H, S-CH_2), 5.72 (s, 2H, N-CH_2), 7.23-8.25 (12H, Ar-<u>H</u>); ^{13}C NMR, δ ($CDCl_3$), 39.63 (S-CH_2), 49.70 (N-CH_2), 55.55 (OCH_3), 114.72 (CH), 115.19 (CH), 120.02 (C), 126.45 (CH), 127.63 (CH), 129.37 (C), 130.32 (CH), 134.68 (CH), 146.28 (C), 155.48 (C_2), 159.23 (C_4), 164.12 (C), 164.52 (C), 186.38 (C=O), 190.93 (C=O).

Ethyl{[3-(2-ethoxy-2-oxoethyl)-4-oxo-3,4-dihydroquinazolin-2-yl]thio}acetate (2h). White crystals from ethanol; $C_{16}H_{18}N_2O_5S$ (350.40), Calcd.: C, 54.85, H, 5.18, N, 7.99; found: C, 54.69, H, 5.19, N, 8.05; yield 75%; m. p. 249 °C; IR, 1557, 1680, 1741, 2927, 2983; ^{1}H NMR, δ ($CDCl_3$), 1.34 (txt, 6H, 2xCH_3), 4.11 (s, 2H, S-CH_2), 4.32 (qxq, 4H, 2xO-CH_2), 4.98 (s, 2H, N-CH_2), 7.45, 7.57, 7.76, 8.25, (4H, Ar-<u>H</u>); ^{13}C NMR, δ ($CDCl_3$), 14.08 (CH_3), 14.18 (CH_3), 34.63 (S-CH_2), 44.98 (N-CH_2), 61.96(OCH_2), 62.09 (OCH_2), 118.99 (C), 126.15 (CH), 127.12 (CH), 134.67 (CH), 147.13 (C), 154.38 (C_2), 161.36 (C_4), 166.76 (C=O), 168.19 (C=O).

S-[3-(Chloroacetyl)-4-oxo-3,4-dihydroquinazolin-2-yl]chloro-ethanethioate (2i). White crystals from ethanol; $C_{12}H_8Cl_2N_2O_3S$ (331.18), Calcd.: C, 43.52, H, 2.43, N, 8.46; found: C, 43.66, H, 2.55, N, 8.41; yield 78%; m. p. 215 °C; IR, 1572, 1701, 3074; ^{1}H NMR, δ ($CDCl_3$), 2.57 (s, 2H, NCOC<u>H</u>$_2$), 3.20 (s, 2H, SCOC<u>H</u>$_2$), 7.43, 7.60, 7.78, 8.29, (4H, Ar-<u>H</u>); ^{13}C NMR, δ ($CDCl_3$), 43.98 (NCO<u>C</u>H_2), 46.12 (SCO<u>C</u>H_2), 118.67 (C), 125.13 (CH), 127.96 (CH), 128.77 (CH), 148.75 (C), 157.90 (C_2), 158.67 (C_4), 164.34 (NCO), 191.58 (S-CO).

2,3-Dihydro-5H-[1,3]thiazolo[2,3-b]quinazolin-5-one (3a). White crystals from Pet. Ether 60-80°; $C_{10}H_8N_2OS$ (204.25), Calcd.: C, 58.81, H, 3.95, N, 13.72; found: C, 58.76, H, 4.09, N, 13.91; yield 63%; m. p. 63-65 °C; IR, 1566, 1626, 1690, 3075; ^{1}H NMR, δ ($CDCl_3$), 3.45 (txt, 2H, S-C$\underline{H}_2$), 4.43 (txt, 2H, N-C$\underline{H}_2$), 7.24, 7.38, 7.54, 8.01, (4H, Ar-$\underline{H}$); ^{13}C NMR, δ ($CDCl_3$), 26.32 (S-$\underline{C}H_2$), 48.57 (N-$\underline{C}H_2$), 119.97 (C), 126.23 (CH), 127.39 (CH), 127.88 (CH), 134.75 (CH), 149.13 (C), 159.62 (C), 161.14 (C=O).

3,4-Dihydro-2H,6H-[1,3]thiazino[2,3-b]quinazolin-5-one (3b). White crystals from Pet. Ether 60-80° C; $C_{11}H_{10}N_2OS$ (218.28), Calcd.: C, 60.53, H, 4.62, N, 12.83; found: C, 60.59, H, 4.65, N, 12.89; yield 83%; m. p. 90-92 °C; IR, 1607, 1676, 2934; ^{1}H NMR, δ ($CDCl_3$), 2.33(m, 2H, C$\underline{H}_2$), 3.23 (t, 2H, S-C$\underline{H}_2$), 4.21 (t, 2H, N-C$\underline{H}_2$), 7.36, 7.51, 7.69, 8.18 (4H, Ar-$\underline{H}$); ^{13}C NMR, δ ($CDCl_3$), 23.14 (CH_2), 27.91 (S-$\underline{C}H_2$), 41.73 (N-$\underline{C}H_2$), 119.38 (C), 125.63 (CH), 125.74 (CH), 126.92 (CH), 134.61 (CH), 147.34 (C), 153.94 (C), 161.48 (C=O).

5H-[1,3]Thiazolo[2,3-b]quinazolin-3,5(2H)-dione (4). Yellow crystals from ethanol; $C_{10}H_6N_2O_2S$ (218.24), Calcd.: C, 55.04, H, 2.77, N, 12.84; found: C, 55.14, H, 2.66, N, 12.92; yield 51%; m. p. 251 °C (dec.); IR, 1581, 1683, 1692, 2971; ^{1}H NMR, δ (Aceton-d_6), 4.11(s, 2H, C$\underline{H}_2$), 7.42-8.13 (4H, Ar-$\underline{H}$); ^{13}C NMR, δ ($CDCl_3$), 34.64 (CH_2), 121.73 (C), 125.12 (CH), 127.87 (CH), 135.23 (CH), 147.29 (C), 159.41 (C), 161.54 (C), 170.74 (C=O).

Results and Discussion

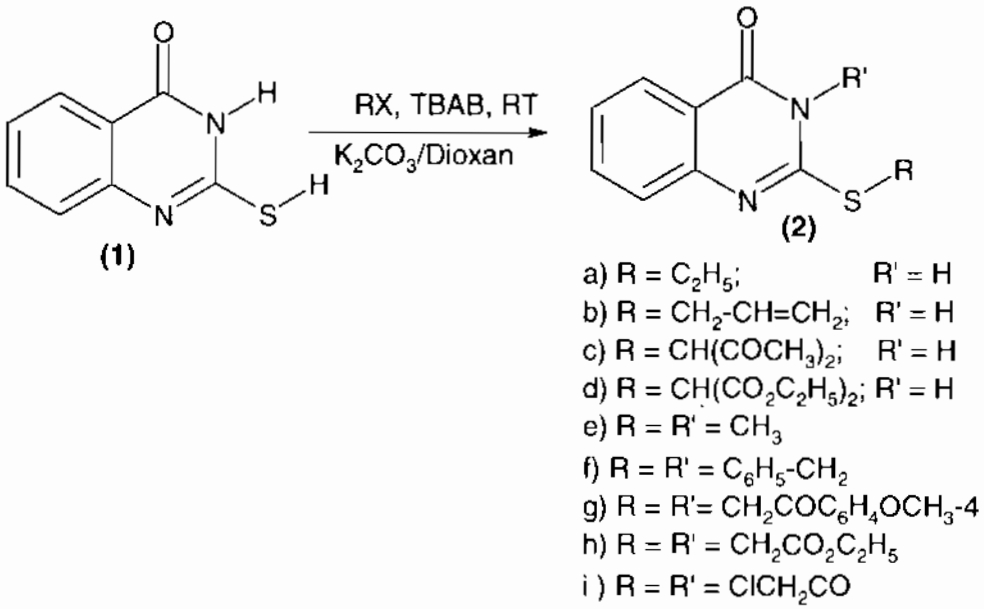
The approach reported here is an extension and continuation of the authors interest in alkylation of some heterocycles uender phase-transfer catalysis (PTC) conditions[18,19]. This work is aiming to study the reactivity of S- versus N- alkylation of 2-mercaptoquinazolin-4(3H)-one (**1**) via solid/liquid PTC conditions by some mono- and dihologen organic reagents as an efficient recent alkylation technique. Also, it is expected that the alkylated products might have biological and medicinal activities in analogy to the well known biologically active quinazolin-4(3H)-one derivatives.

Spectral data proved that 2-mercaptoquinazolin-4(3H)one (**1**) is existed in lactam form, then the expected PTC-alkylation will be either in S- or N- atoms to give monoalkylated product or it occures in both S- and N- to give the dialkylated product.

The electronegativity difference of sulfur and nitrogen predomenates, exclusiovely, S-alkylation rather than N-alkylation [19-22].

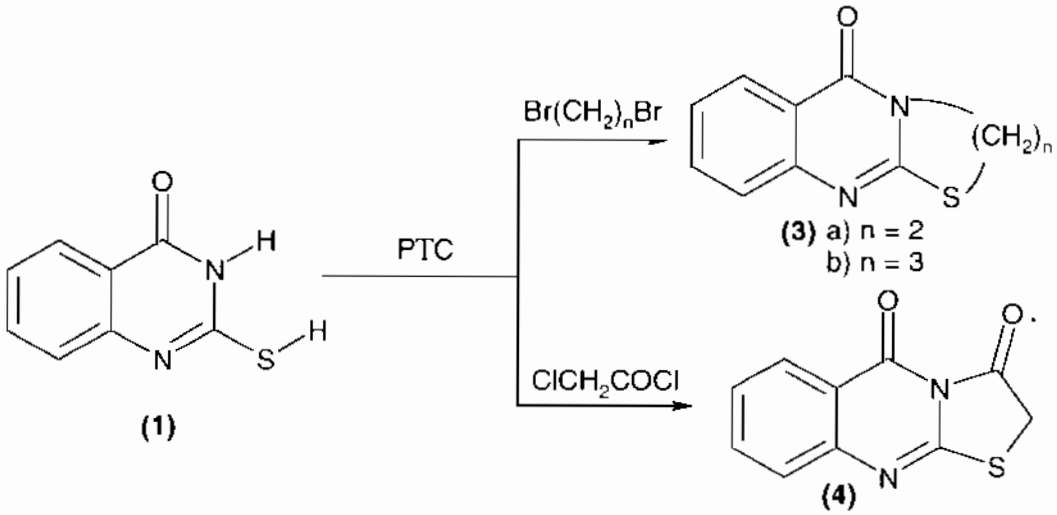
The optimized reaction conditions of PTC - alkylation are the treatment of 2-mercaptoquinazolin-4(3H)-one (**1**) with haloorganic reagents in dioxane / anhydrous potasstium carbonate as liquid / solid phases in the presence of tetrabutylammonium bromide (TBAB) as catalyst with efficient stirring for 2-4 hr at 25 °C.

Treatment of 2-mercaptoquinazolin-4(3H)-one (**1**) with ethyl bromide, allyl bromide, bromoactylacetone and diethyl bromomalonate in 1:3 molar ratio, respectively, under the optimized PTC reaction conditions afforded, exclusively, S-monoalkylation to give **2a-d**, while with methyl iodide, benzyl bromide, ω-bromo-4-methoxyacetophenone, ethyl bromoacetate, chloroacetyl chloride underwent, simultaneous, S- and N-dialkylation to give **2 e-i**, respectively (Scheme **1**).



Scheme 1

On the other hand, under the same optimized PTC conditions treatment of an equimolar amount of 2-mercaptoquinazolin-4(3H)-one (**1**) and dihalogen organic reagents such as 1,2-dibromoethane, 1,3-dibromopropane and chloroacetyl chloride underwent S- and N- cycloalkylation to give 2,3-dihydro-5H-[1,3]thiazolo[2,3-b]quinazolin-5-one (**3a**), 3,4-dihydro -2H, 6H-[1,3]thiazino[2,3-b]quinazolin-6-one (**3b**) and 5H-[1,3]-thiazolo-[2,3-b]quinazolin-3,5(2H)-dione (**4**), respectively (Scheme **2**).



Scheme 2

Conclusion

The feasibility study in this work revealed that PTC-alkylation of -mercaptoquinazolin-4(3H)-one (**1**) proceeds smoothly in a moderate yield (60-85%) and occurs in all cases, predominantly, at S- with monohalogen compounds, while, simultaneous, S- and N- dialkylations of some cases. Also, PTC-cycloalkylations was afforded with dihalogen organic reagents to give annulated heterocyclic systems such as thiazoloquinolinone and thiazinoquinolinone derivatives.

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تفاعلات حفز الانتقال الصنفي بالألكلة والألكلة التحلقية على مركبات ٢-الميركابتوكينوزولين-٤(H٣)أون

علي خليل

قسم الكيمياء ، كلية العلوم ، جامعة عين الشمس ، القاهـــــرة – مصر

المستخلص. تمت ألكلة ٢-مركبتوكينازولين-٤-ون باستخدام بعض الكواشف العضوية الهالوجينية تحت ظروف حفز الانتقال الصنفي فى وجود بروميد رباعي بيوتيل أمونيوم كحافز وتحت درجة حرارة الغرفة ، حيث تتم الألكلة الأحادية بصفة رئيسية على الكبريت وفي بعض الأمثلة تمت الألكلة الثنائية على كل من الكبريت والنتروجين. وعند استخدام الكواشف ثنائية الهالوجين فتتم الألكلة مع الحولقة لتعطي مركبات عديدة الحلقات الملتحمة .