Tetrahedron Vol. 40, No. 23, pp. 4937 to 4939, 1984
Printed in Great Britain.

0040-4020/84 $3.00 + .00

EXTRUSION REACTIONS—VI[1]

TRANSFORMATIONS OF BETA (4-QUINAZOLINYLTHIO) KETONES TO 3-(BETA KETOALKYL)-4(3H)-QUINAZOLONE DERIVATIVES

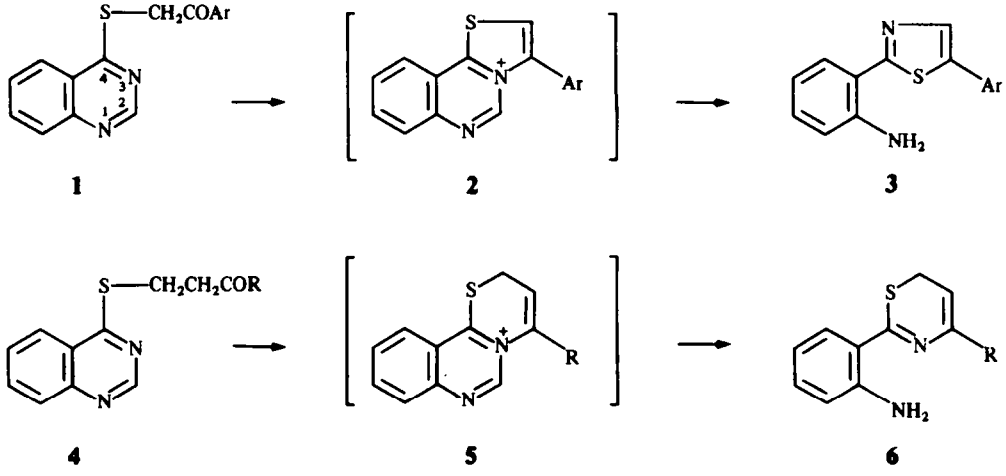
HARJIT SINGH* and KANWAL DEEP†
Department of Chemistry, Guru Nanak Dev University, Amritsar 143 005, India

(*Received in UK* 19 *April* 1984)

Abstract—4-(4-Quinazolinylthio)-butan-2-one and 3-(4-quinazolinylthio) propiophenone (**4**, R = CH_3, C_6H_5) with $POCl_3$ give 3-(3-oxobutyl)-4(3H)-quinazolone and 3-(2-benzoylethyl)-4(3H)-quinazolone (**7**, R = CH_3, C_6H_5, X = O) via S → N rearrangement followed by >C=S to >C=O conversion. Non-protic heterocyclic thioamides undergo similar oxidation.

2-(4-Quinazolinylthio) acetophenones (**1**) with sulphuric acid–PPA undergo mainly S-extrusion[2] but with conc HCl or $HClO_4$,[3–5] give 2-(*o*-aminophenyl) thiazoles (**3**) through hydrolytic extrusion of C(2) of quinazoline moiety of the first formed thiazolo[3,2-c] quinazolinium cation (**2**). 3-(4-Quinazolinylthio (ketones (**4**, R = CH_3, C_6H_5) on similar reaction could provide 2-(*o*-aminophenyl)-6H-1,3-thiazine derivatives (**6**). Phosphoryl chloride, a better cyclodehydrating agent, might accomplish cyclodehydration of **4** to **5** which could provide **6**. It has been found that in these reactions instead of the envisaged ring transformation, 3-(betaketoalkyl)-4(3H)-quinazolines (**7**, X = O) are formed.[6] $POCl_3$ has further been found to perform >C=S to >C=O conversion in non-protic heterocyclic thioamides.

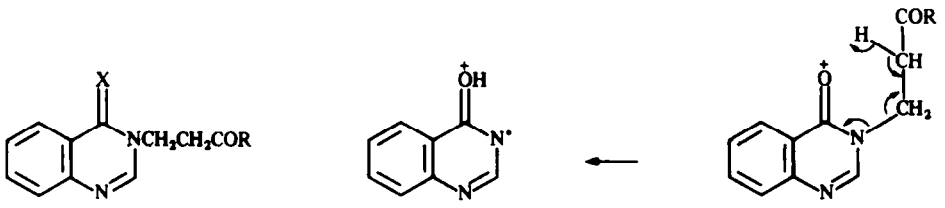
The parent ion peak at $M^{+\cdot}$ *m/e* 216 in the mass spectrum and elemental analysis suggest a molecular formula $C_{12}H_{12}N_2O_2$. Irs ^{1}H-NMR signals at δ 2.17 (s, 3H,CH_3), 3.07 (t, 2H,CH_2), 3.25 (t, 2H,CH_2), 7.30–8.00 (m, 4H, ArH) and 8.80 (s, 1H, C(2)H) are consistent with the structural unit $—CH_2CH_2COCH_3$ and a quinazoline ring. The IR spectrum exhibits two CO absorption bands at 1690 and 1655 cm^{-1} as against one CO absorption band at 1700 cm^{-1} in the precursor. Obviously, the additional CO group has been created at C(4) by the replacement of the S by O, a situation which necessitates the shifting of the 3-oxobutyl moiety. The presence of 3-oxobutyl group at N(3) is evident from the mass spectrum base peak at *m/e* 146 for the cation (**8**) which can be formed as a result of beta cleavage via McLafferty rearrangement (**9**) which is only possible if the 3-oxobutyl group is present at N(3)



RESULTS AND DISCUSSION

4-(4-Quinazolinylthio)butan-2-one (**4**, R = CH_3) on refluxing in phosphoryl chloride ($POCl_3$) gives three products. The major product, R_f 0.74 ($CHCl_3$–CH_3OH, 10:2), m.p. 76° (40%), is devoid of elemental S. of quinazoline-4-one system. Thus this component has been assigned the structure, 3-(3-oxobutyl)-4(3H) quinazolone (**7**, R = CH_3, X = O) which is corroborated by its comparison with an authentic sample procured from quinazoline-4(3H)-one and 4-chlorobutan-2-one and the ^{13}C-NMR spectrum. The other two products are quinazoline-4(3H)-thione (R_f 0.40; 15%) and quinazoline-4(3H)-one (R_f 0.34; 20%). Similarly, 3-(4-quinazolinylthio)propiophenone (**4**,

† Present address: Malti-Chem Research Centre, Nandesari, Baroda, India.



7 8 9

$R = C_6H_5$) gives 3-(2-benzoylethyl)-4(3H)-quinazolone (7, $R = C_6H_5$, X = O) as the major product (60%). On performing these reactions in $POCl_3$ containing polyphosphoric acid, similar results are obtained. Ethyl beta (4-quinazolinylthio)propionate (4, $R = OC_2H_5$) with $POCl_3$ as well as $POCl_3$—PPA gives only quinazoline-4(3H)-one.

2-(4-Quinazolinylthio)acetophenones (1) with $POCl_3$ followed by aqueous sodium bicarbonate treatment give 2-(*o*-aminophenyl)-4-arylthiazoles,[4] in yields better than those obtained with conc HCl—$HClO_4$. Thus we find that 2-(4-quinazolinylthio)acetophenones (1) which form thiazolo[3,2-c]quinazolinium cations (2), on hydrolytic C(2) extrusion, provide derivatives of 3 but beta (4-quinazolinylthio)ketones (4) which in a similar sequence of steps envisage the formation of relatively less stable 2H, 1,3-thiazino[3,2-c]quinazolin-5-ium cations (5), undergo an alternate 1,3-migration of the chain attached at S in 4 to N(3) of quinazoline in analogy with similar ethers[8] and the resulting >C=S is transformed to >C=O to form 3-(betaketoalkyl)-4(3H)-quinazolones (7, X = O).

In order to investigate the above postulate, 3-(3-oxobutyl)quinazoline-4(3H)thione (7, $R = CH_3$, X = S) was prepared from 3-(3-oxobutyl)-4-(3H)-quinazolone (7, $R = CH_3$, X = O)[6] and phosphorus pentasulphide in dry pyridine. On monitoring the reaction of 4-(4-quinazolinylthio)butan-2-one (4, $R = CH_3$) with $POCl_3$ through TLC, it has been found that 3-(3-oxobutyl)quinazoline-4(3H)-thione (7, $R = CH_3$, X = S) is formed as a minor product (TLC), but it would not be isolated. However, 7 ($R = CH_3$, X = S), on refluxing in $POCl_3$ is converted into 3-(3-oxobutyl)-4(3H)-quinazolone (7, $R = CH_3$, X = O) in 45% yield. Subsequently, to confirm the formation of 7 ($R = CH_3$, X = O) as a result of thermal migration of 3-oxobutyl moiety from S in 4 ($R = CH_3$) to N(3) of quinazoline ring, we have heated 4 ($R = CH_3$) in xylene or DMF and 7 ($R = CH_3$, X = S) has been isolated in 40% and 25% yields respectively. It may be concluded that the conversion of beta(4-quinazolinylthio)ketones (4) to 3-(betaketoalkyl)-4(3H)-quinazolones (7, X = O) takes place by a sequence of thermally induced conversion of 4 to 7 (X = S), followed by the conversion of >C=S to >C=O to form 7 (X = O). In order to investigate whether the O in >C=O formed from >C=S stems from $POCl_3$, we tried to isolate $PSCl_3$, in the mixture, but all attempts in this direction failed.

In order to investigate whether these rearrangement reactions are characteristic of a 3-ketoalkyl moiety present at S of quinazoline-4(3H)-thione or whether analogous compounds possessing any other group incapable of intermolecular condensation would also undergo such a transformation, it has been found that with $POCl_3$, 4-benzylthioquinazoline[9] provides 3-benzyl-4(3H):quinazolone in 40% yield.

The oxidizing character of phosphoryl chloride for the conversion of $-\overset{|}{C}=S$ to $-\overset{|}{C}=O$ is unprecedented. We have also found that 3-benzylquinazoline-4(3H)thione[9] and 1-methylpyrrolidine-2(1H)-thione on refluxing in $POCl_3$ give 3-benzyl-4(3H) quinazolone and 1-methyl-2(1H)-pyrrolidone in 70% and 40% yields respectively.

EXPERIMENTAL

For general experimental details see ref. 1.

4-(4-Quinazolinylthio)butan-2-one (4, $R = CH_3$)

A soln of 4-chlorobutan-2-one (0.01 mol) in EtOH (10 ml) was added to a soln of quinazoline-4(3H)-thione (0.01 mol) in 2% NaOH aq and the mixture was vigorously stirred for 2 hr. The product separated was crystallized from EtOH, 75%, m.p. 110°. IR ($CHCl_3$): 1700 cm^{-1} (CO). ^{1}H-NMR ($CDCl_3$): δ 2.12 (s, 3H, CH_3), 3.12 (t, 2H, CH_2), 4.51 (t, 2H, CH_2), 7.55–8.66 (m, 5H, ArH). (Found: N, 12.10; S, 13.80. Calc. for $C_{12}H_{12}N_2OS$: N, 12.06; S, 13.87%). The data of compounds obtained similarly from quinazoline-4(3H)-thione and *β*-chloropropiophenone—ethylchloropropionate are given below:

Compound 4 ($R = C_6H_5$). Yield 85%, m.p. 135° (EtOH). IR ($CHCl_3$): 1700 cm^{-1} (CO). ^{1}H-NMR ($CDCl_3$): δ 3.65 (t, 2H, CH_2), 4.8 (t, 2H, CH_2), 7.50–8.40 (m, 10H, ArH). (Found: C, 64.30; H, 4.75; N, 9.00; S, 10.84. Calc for $C_{17}H_{14}N_2OS$: C, 69.38; H, 4.76; N, 9.36; S, 10.88%.)

Compound 4 (R=OEt). Yield 60%, m.p. 75° ($CHCl_3$). IR ($CHCl_3$): 1720 cm^{-1} (CO). ^{1}H-NMR ($CDCl_3$): δ 1.25 (t, 3H, CH_3), 3.07 (t, 2H, CH_2), 4.15 (q, 2H, CH_2), 4.77 (t, 2H, CH_2), 7.7–8.87 (m, 5H, ArH). (Found: N, 10,65; S, 11.90. Calc for $C_{13}H_{14}N_2O_2S$: N, 10.68: S, 11.73%.)

Reactions of (4-quinazolinylthio)ketones with $POCl_3$

General procedure: A suspension of (4-quinazolinylthio) ketone (0.01 mol) in $POCl_3$ (30 ml) was refluxed. The progress of the reaction was monitored by TLC of the $CHCl_3$ extract of an aliquot portion after neutralization with $NaHCO_3$. The reaction was completed in 5–7 hr. $POCl_3$ was distilled off under reduced pressure and the residue was neutralized with $NaHCO_3$ aq, extracted with $CHCl_3$, the extract was dried over Na_2SO_4 and then $CHCl_3$ was distilled off. The residue was chromatographed on silica gel using benzene—$CHCl_3$—EtOAc (10:2:1) as eluent. In case of 4 (R = aryl), products separated at $NaHCO_3$ aq treatment stage and were collected.

(a) 4-(4-Quinazolinylthio)butan-2-one (4, $R = CH_3$) with $POCl_3$ furnishes 3-(3-Oxobutyl)-4(3*H*)-quinazolone (7, $R = CH_3$, X = O), yield 45%, m.p. 76° (EtOH). IR ($CHCl_3$):

1655, 1690 cm^{-1} (CO). ^{1}H-NMR ($CDCl_3$): δ 2.17 (s, 3H, CH_3), 3.07 (t, 2H, CH_2), 4.25 (t, 2H, CH_2), 7.3–8.4 (m, 5H, ArH). ^{13}C-NMR ($CDCl_3$): δ 30.040 (q, CH_3), 41.324 (t, CH_2), 43.556 (t, CH_2), 121.245 (s, ArC), 124.748 (d, ArCH), 127.104 (d, ArCH), 128.344 (d, ArCH), 135.257 (d, ArCH), 143.503 (d, ArCH), 149.270 (S, ArC), 160.058 (s, CO), 205.846 (s, CO). Mass: M^+ *m/e* 216 ($C_{12}H_{12}N_2O_2$). (Found: C, 66.60; H, 5.40; N, 13.00. Calc for $C_{12}H_{12}N_2O_2$: C, 66.66; H, 5.55; N, 12.95%.)

Yields: quinazoline-4(3H)-thione, 15%; quinazoline-4(3H)-one, 20%.

(b) 3-(4-Quinazolinylthio)propiophenone (**4**, R = C_6H_5) with $POCl_3$ furnishes 3-(2-benzoylethyl)-4(3H)-quinazolone (**7**, R = C_6H_5, X = O), yield 60%, m.p. 125° ($CHCl_3$). IR ($CHCl_3$): 1688, 1692 cm^{-1} (CO). ^{1}H-NMR ($CDCl_3$): δ 3.60 (t, 2H, CH_2), 4.42 (t, 2H, CH_2), 7.25–8.37 (m, 9H, ArH). Mass: M^+ *m/e* 278 ($C_{17}H_{14}N_2O_2$). (Found: C, 77.30; H, 4.87; N, 11.0. Calc for $C_{17}H_{14}N_2O_2$: C, 77.38; H, 5.03; N, 10.71%.)

Yields: quinazoline-4(3H)-thione, 10%; quinazoline-4(3H)-one, 10%.

(c) 4-Methyl-2-(4-quinazolinylthio)acetophenone (**1**, R = *p*-$CH_3C_6H_4$) with $POCl_3$ furnishes 2-(*o*-Aminophenyl)-4-tolylthiazole (**3**, R = *p*-$CH_3C_6H_4$), yield 85%, m.p. 108° (EtOH). IR ($CHCl_3$): 3200, 3400 cm^{-1} (NH_2). ^{1}H-NMR (CCl_4): δ 2.5 (s, 3H, CH_3), 5.65 (s, 2H, NH_2, exchangeable with D_2O), 6.70 (b, 1H, CH), 7.28–7.80 (m, ArH). Mass: M^+ *m/e* 266 ($C_{16}H_{14}NS$).

(d) 2-(4-Quinazolinylthio)acetophenone (**1**, R = C_6H_5) with $POCl_3$ furnishes 2-(*o*-aminophenyl)-4-phenylthiazole (**3**, R = C_6H_5),[4] yield 80%.

3-(3-Oxobutyl)-quinazoline-4(3H)-thione (**7**, R = CH_3, X = S)

A suspension of **7** (R = CH_3, X = O) (0.01 mol), P_2S_5 (0.01 mol) in dry pyridine (100 ml) was refluxed. The reaction was completed in 9 hr (TLC). Pyridine was removed under reduced pressure and the residue was neutralized with $NaHCO_3$ aq. The solid separated was purified by chromatography on silica gel using first $CHCl_3$ and then $CHCl_3$–EtOAc (10:3) as eluents. Yield 45%, m.p. 210°. IR ($CHCl_3$): 1660 cm^{-1} (CO). Mass: M^+ *m/e* 232 ($C_{12}H_{12}N_2OS$).

Acknowledgements: We thank Prof. P. J. Scheuer, University of Hawaii for mass and ^{13}C-NMR spectra and UGC (India) for financial assistance.

REFERENCES

[1] Part V. H. Singh, P. Singh and N. Malhotra, *J. Chem. Soc. Perkin Trans.* 1, 2647 (1981).
[2] H. Singh, C. S. Gandhi and M. S. Bal, *Heterocycles* **14**, 3 (1980).
[3] H. Singh, C. S. Gandhi and M. S. Bal, *Chem. Ind.* 420 (1980).
[4] H. Singh, C. S. Gandhi and M. S. Bal, *Indian J. Chem.* **20B**, 17 (1981).
[5] 6-Methyl-4-quinazolinylthioacetophenones unsubstituted at C(2), via a similar sequence give 2-acetonyl-4-arylthiazole derivatives. H. Singh, S. K. Aggarwal and N. Malhotra, *Heterocycles* **22**, 353 (1984).
[6] M. S. Bal, K. Deep and H. Singh, *Indian J. Chem.* **21B**, 805 (1982).
[7] P. Singh, K. Deep and H. Singh, *J. Chem. Res.* in press.
[8] R. J. Grout and M. W. Patridge, *J. Chem. Soc.* 3549 (1960).
[9] J. Tulecki and J. Kalinowska, *Torz. Ann. Pharm.* **6**, 69 (1967); *Chem. Abst.* **71**, 112881 k (1969).