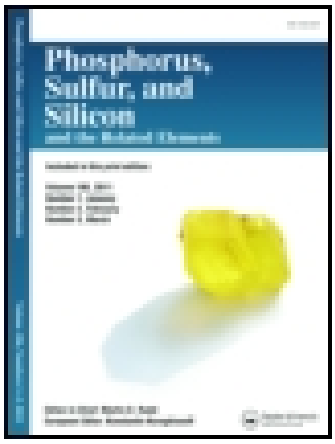

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Synthesis of benzoxazolylthiomethyl and benzthiazolylthiomethyl quinazolin-4(3H)-ones

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Synthesis of benzoxazolylthiomethyl and benzthiazolylthiomethyl quinazolin-4(3*H*)-ones

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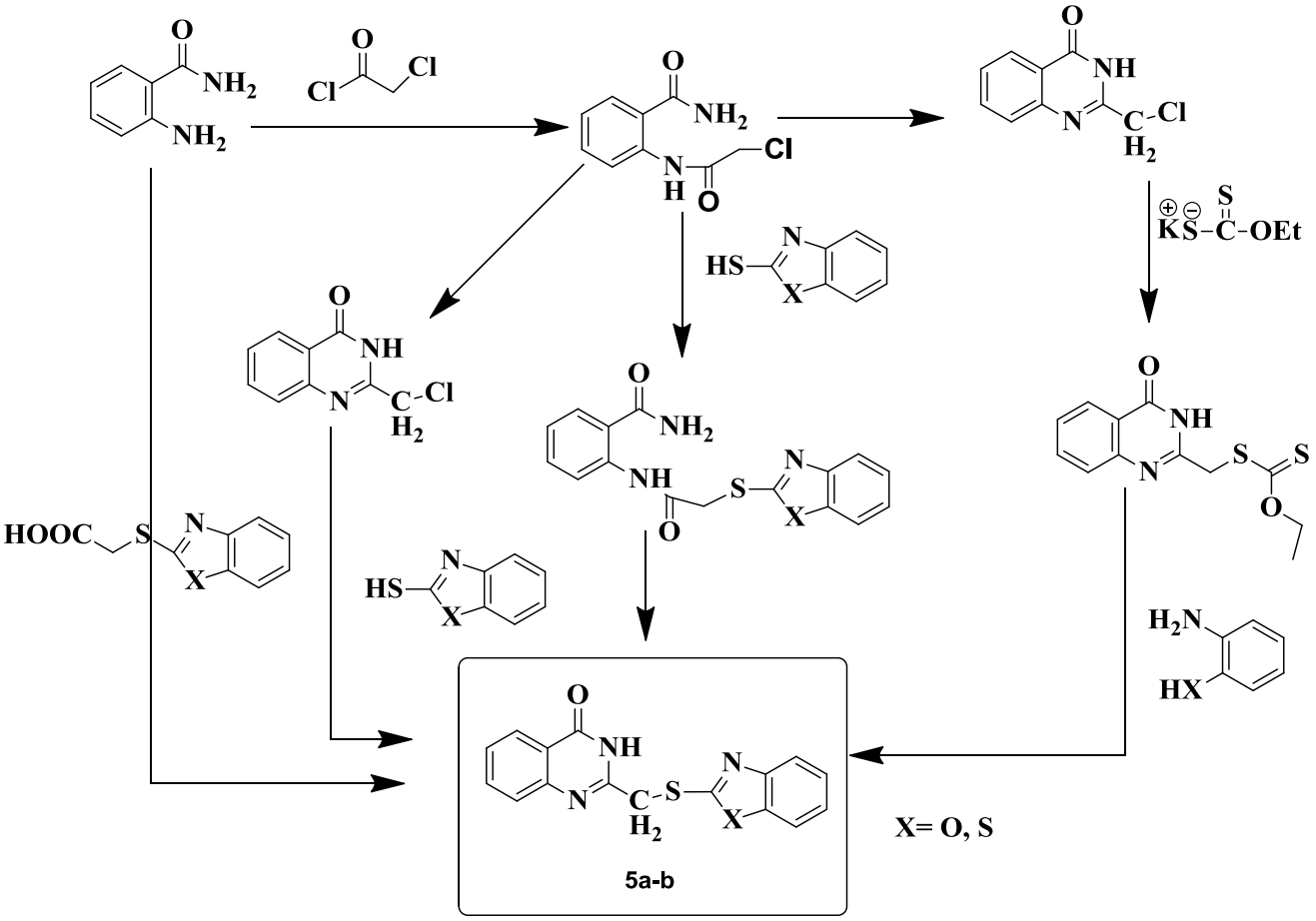
Abstract: *o-Aminophenol (**1a, X=O**) or o-aminothiophenol (**1b, X=S**) was reacted with carbon disulfide in ethanol containing KOH under reflux to obtain 2-mercaptobenzoxazole (**2a, X=O**) and 2-mercaptobenzthiazole (**2b, X=S**) respectively. Condensation of* **2a** *and* **2b** *each with chloroacetic acid gave 2-(benzoxazol-2-ylthio)acetic acid **(3a, X=O)** and 2-(benzthiazol-2-ylthio)acetic acid **(3b, X=S)** respectively which with anthranilamide gave 2-((benzoxal-2-ylthio)methyl) quinazolin-4(3H)-one (**5a, X=O)** and 2-((benzthiazol-2-ylthio)methyl)quinazolin-4(3H)-one(**5b, X=S**) respectively. The products **5a-b** could be prepared in three other routes involving the general sequences* **6 → 2 → 5, 6 → 7 → 5** and **8 → 9 → 5.**



Key words: Anthranilamide, quinazolin-4(3*H*)-one, benzoxazole, benzthiazole, TBAB

Introduction

The quinazolinone ring system forms an important class of N-heterocyclic compounds as it is present in a large number of compounds with useful biological properties such as anti-inflammatory[1-2], anticonvulsant[3], hypotensive[4] and anti-malarial[5] types. 2-Thioquinazolinones possess good analgesic activities[6]. 2-Heterylquinazolin-4(3*H*)-ones exhibit a wide range of pharmacological properties[7, 8], such as good antimicrobial activity against different species of gram-positive bacteria[9], gram-negative bacteria[10] and pathogenic fungi[11, 12] . In view of this wide range of pharmacological activities, the quinazolinone derivatives have been the target of a large number of organic synthetic efforts[13-16].

It was reported from our laboratory earlier[17] that treatment of 2-(4-oxo-3,4-dihydro-quinazolin-2-ylsulfanyl)-propionic acid with with *o*-phenylenediamine in refluxing 6N aq.HCl for 12 h gave 2-[1-(1*H*-benzimidazol-2-yl)-ethylsulfanyl] quinazolin-4(3*H*)-one. In another report[18], also from our laboratory, condensation of 2-((chloromethyl) quinazolin-4(3*H*)-One with 2-mercaptoquinazolin-4(3*H*)-one in dimethylformamide containing K_2CO_3 as a base and TBAB as a phase transfer catalyst for 2-3 h gave bisquinazolin-4(3*H*)-one derivatives i.e 2-(4-Oxo-3,4-dihydroquinazolin-2-ylsulfinylmethyl)quinazolin-4(3*H*)-one. Patil[19] *et al.* synthesized 2-substituted-1*H*-benz(d)imidazol-2-ylsulfinyl)methyl-3-substitutedquinazolin-4(3*H*)-ones by condensing 2-chloromethylquinazolin-4(3*H*)-one with 2-mercaptobenzimidazole in 5N NaOH dissolved in ethanol as a solvent for 10-12 h.

In view of the literature information given above, it seems only limited work has been done on the preparation of 2-alkylthioheteryl derivatives of quinazolin-4(3*H*)-one. The present

work is concerned with the synthesis of benzoxazolylthiomethyl, benzthiazolylthiomethyl 2-substitutions of quinazolin-4(3*H*)-ones.

Results and discussions

Commercially available *o*-aminophenol (**1a**) or *o*-aminothiophenol (**1b**) were each treated, independently, with carbon disulfide in isopropyl alcohol containing KOH giving benzo[d]oxazole-2-thiol(**2a**) or benzo[d]thiazole-2-thiol(**2b**) respectively by reported[20-22] procedure. The latter, were, again, reacted with 2-chloroacetic acid in aq. KOH at RT for 1 h giving (benzo[d]oxazol-2-ylthio) acetic acid **(3).** The structures of all new compounds synthesized in this work have been established on the basis of their spectroscopic data. (Experimental).

Condensation of **3a** (i.e. **3**, X=O) with anthranilamide (**4**) under refluxing conditions in aq. HCl for 10 h gave a product which has been characterized as 2-((benzo[d]oxazol-2-ylthio)methyl)quinazolin-4(3*H*)-one (**5a**).

In an alternative approach, reaction of **2** with **6** under different conditions in the presence of bases at RT for 3-4 h gave **5,** which were found to be identical in m.p., m.m.p., TLC and IR with that of the same products obtained in the route described above, (i.e. **3**+ **4** ⟶ **5**).

The preparation of **5** from **2** and **6** has been studied under different conditions and the results are shown in Table 1.

It is obvious from **Table 1**, that for the condensation of **2(a-b)** with **6,** 5% methanolic NaOH seems to offer the best conditions giving **5** in the highest yield.

In a yet alternative approach, **5** could be prepared by the condensation of dithiocarbonic acid o-ethyl ester i.e. S-[2-(4-oxo-3, 4-dihydroquinazolin-2-yl) ethyl] ester (**7**) with **1** in refluxing toluene containing traces of acetic acid as catalyst for 2-3 h. The former compound. i.e. **7,** in turn, was synthesized by the reaction of 2-chloromethylquinazolin-4(3*H)*-one (**6**) with potassium *o*-ethyl dithiocarbonate in ethanol at RT for 3 h. (Scheme 1).

The conversion of **7** to **5** seems to follow the mechanism given in Scheme 2

The mechanism seems to follow the strategy as reported[17] earlier in the case of condensation of **7** with *o*-phenylenediamine. Here, the nucleophilic attack by the amino group of **1** on the xanthate carbon of **7** yielding the intermediate **7A** that loses of ethanol to form **7B.** The latter, then, undergoes ring closure involving a second but intramoleular, nucleophilic attack by the hydroxyl/thio group on the xanthate carbon to form **7C** which changes to **7D.** This intermediate then undergoes loss of elements of H_2S in a bid to aromatize to form the final product **5.**

In another alternative method, **5** could also be synthesized from **4** by reaction with chloroacetyl chloride in benzene, triethylamine as catalyst at RT for 1-2 h yielding 2-(2-chloroacetylamino)benzamide (**8)** which on treatment with **2** in aq. K_2CO_3 gave **9** followed by refluxation in acetic acid for 3 h as shown in **Scheme 1**.

Experimental section

Melting points are uncorrected and were determined in open capillary tubes in sulphuric acid bath. TLC was run on silica gel – G and visualization was done using iodine or UV light. IR

spectra were recorded using Perkin – Elmer 1000 instrument in KBr pellets. ^{1}H NMR spectra were recorded in DMSO – d_6 using TMS as internal standard using an instrument operating at 400 MHz.

Preparation of 3 from 2

A mixture of 2-mercaptobenzoxazole (**2a, X=O**) and 2-mercaptobenzthiazole (**2b, X=S**) (10 mmol), 2-chloroacetic acid (10 mmol), K_2CO_3 (10 mmol) and DMF (10 mL), TBAB as a PTC was stirred for 1-2 h at RT. After completion of reaction, the mixture was cooled to RT and treated with acetic acid until neutralised. The separated solid was filtered, washed with water (2×40 mL) and dried to obtain crude **3a-b.** The latter on recrystallization from suitable solvent gave pure **3a-b.**

3a: white colour solid (1.55 g, 73 %), M.p. 178-80 $^\circ$C; IR (KBr): 3200-3000 cm^{-1} (broad, –NH-), 1700, 1665 cm^{-1} (strong, sharp, C=O); ^{1}H-NMR (DMSO-d_6/TMS): δ 4.00 (s, 2H, -C**H$_2$**-), 7.30-8.00 (m, 4H, **aryl protons**), 12.75 (s, 2H, D_2O exchangeable protons, –N**H**- and –COO**H**); LC-MS: m/z 210[M+H]$^+$. Elemental Analysis: C, 51.67; H, 3.37; N, 6.69; O, 22.94; S, 15.33. Found: C, 51.64; H, 3.35; N, 6.73; O, 22.91; S, 15.36.

3b white colour solid (1.85 g, 80 %), M.p. 226-227 $^\circ$C (228-230 $^\circ$C lit); IR (KBr): 3200-3000 cm^{-1} (broad, –NH-), 1700, 1665 cm^{-1} (strong, sharp, two, C=O); ^{1}H-NMR (DMSO-d_6/TMS): δ 4.10 (s, 2H, -C**H$_2$**-), 7.20-8.00 (m, 4H, **aryl protons**), 12.65 (s, 2H, D_2O exchangeable protons, –N**H**- and –COO**H**); LC-MS : m/z 224 [M+H]$^+$. Elemental Analysis: C, 47.98; H, 3.13; N, 6.22; O, 14.20; S, 28.47. Found: C, 47.95; H, 3.16; N, 6.25; O, 14.22; S, 28.48.

Preparation of 5 from 3 and 4

A mixture of **3** (5 mmol), *o*-aminobenzamide **(4)** (0.68g, 5 mmol) and aq. HCl (6N, 50 mL) was refluxed for 8-10 h. At the end of this period, the reaction mixture was diluted with water (50 mL) and the pH adjusted to ≥ 7.0 with aq. ammonia. The separated solid was filtered, washed with water (2×10 mL) and dried.

5a: Yield=2.5 g (80 %); M.p. =190-192 ^{o}C (MeOH). IR (KBr): 3200 cm^{-1} (–NH), 1657 cm^{-1} (–NHC=O); ^{1}H NMR (DMSO-d_6) δ 4.53 (s, 2H, -C**H$_2$**-), 7.14-8.11 (m, 8H, **aryl protons**), 12.65 (b, s, 1H, D_2O, –N**H**-); ^{13}C-NMR (DMSO-d_6/TMS) δ 34.8(CH_2), 114.0, 121.1, 121.6, 125.8, 126.6, 126.8, 134.4, 139.4, 148.4, 149.7, 153.9 (aromatic carbons) and 161.1(C=O), LCMS: m/z 310 $[M+H]^+$. $C_{16}H_{11}N_3O_2S$, Elemental Analysis: C, 62.12; H, 3.58; N, 13.58; O, 10.34; S, 10.37. Found: 62.09; H, 3.63; N, 13.61; O, 10.32; S, 10.36.

5b: Yield: 2.45 g (76 %); M.p. =163-165 ^{o}C (MeOH); IR (KBr): 3241 cm^{-1} (broad, N**H** & O**H**), 1671 cm^{-1} (strong, C=O); ^{1}H NMR (DMSO-d_6): δ 4.53 (s, 2H, -C**H$_2$**-), 7.14-8.11 (m, 8H, **aryl protons**), 12.65 (broad, s, 1H, D_2O exchangeable proton, –N**H**-); ^{13}C-NMR spectrum (DMSO-d_6/TMS) showed signals at δ 34.3(CH_2), 114.4, 121.1, 121.8, 125.7, 126.5, 126.8, 134.3, 139.5, 148.5, 149.8, 153.8(aromatic carbons) and 161.7(C=O). LC-MS: m/z 325 $[M+H]^+$. Chemical Formula: $C_{16}H_{11}N_3OS_2$, Elemental Analysis: C, 59.06; H, 3.41; N, 12.91; O, 4.92; S, 19.71. Found: C, 59.08; H, 3.39; N, 12.93; O, 4.95; S, 19.66.

Preparation of 5 from 6 and 2 using triethylamine and acetone

A mixture of 2-((chloromethyl) quinazolin-4(3*H*)-One (**6)** (10 mmol), **2** (10 mmol), triethylamine (TEA) (1.6 mL, 10 mmol) and acetone (25 mL) was stirred at RT for 3-4 h. After

completion of the reaction, as monitored by TLC, the mixture was poured into ice-cold water (2×10 mL). The separated product was filtered, washed with water (2×10 mL), dried to obtain. Pure **5a-b** (MeOH), identical in mp, mmp and TLC with that of the same product obtained in the route described above, i.e. **3**+**4** ⟶ **5**.

5a: Yield = 2.4 g (75 %); M.p. = 198-200 ^{o}C (MeOH).

5b: Yield = 2.7 g (83 %); M.p. = 163-165 ^{o}C (MeOH).

Preparation of 5 from 6 and 2 under PTC conditions

A mixture of **6** (1.93, 10 mmol), **2** (10 mmol), K_2CO_3 (1.92 g, 15 mmol), TBAB (5 mmol) as a PTC catalyst and DMF (10 mL) was stirred at RT for 3-4 h. After completion of the reaction, as monitored by TLC, the mixture was poured into ice-cold water (100 mL). The separated product was filtered, washed with water (2×25 mL) and dried to obtain **5a-b**. Pure **5a-b** (MeOH), identical in mp, mmp and TLC with that of the same product obtained in the route described above, i.e. **3**+**4** ⟶ **5**

5a: Yield = 2.30 g (73 %); M.p. = 190-192 ^{o}C (MeOH**).**

5b: Yield = 2.7 g (83 %); M.p. = 163-165 ^{o}C (MeOH).

Preparation of 5 from 7 and 1

A mixture of **7** (2.8g, 10 mmol), **1** (10 mmol), acetic acid (1.2 mL, 10 mmol) and toluene (30 mL) was refluxed at 110 $^{\circ}$C in an oil-bath for 6-8 h, until the reaction was complete as shown by periodic TLC for disappearance of the starting material. At the end of this period, toluene was distilled off and the residue treated with aq. NaOH (1N, 50 mL) at RT. The separated solid was filtered, washed with water (2×15 mL) and dried to obtain **5a-b**. Pure **5a-b** (MeOH), identical in

mp, mmp and TLC with that of the same product obtained in the route described above, i.e. **3**+**4** ⟶ **5**

5a: Yield =2.1 g (77 %), M.p. = 190-192 ^{o}C (MeOH).

5b: Yield = 2.7 g (83 %); M.p. = 163-165 ^{o}C (MeOH).

Preparation of 7 from 6

A mixture of **6** (10 mmol), potassium ethoxydithiocarbamate (10 mmol) and ethanol (30 mL) was refluxed for 2 h. Then, the reaction mixture was cooled to RT and the separated KBr salt was filtered and washed with ethanol (20 mL). The ethanolic filtrate was distilled off and the residue diluted with water (20 mL). The separated solid was filtered, washed with water (20 mL) and dried to obtain crude **7**.

7: Yield: 2.1 g (80 %); M.p.156-158 $^{\circ}$C (157-159 $^{\circ}$C [lit.17]) ; IR (KBr): 3200-3100 cm^{-1} (broad, –NH-), 1660 cm^{-1} (strong, sharp, C=O of the amide group), 1180 cm^{-1} (broad, C=S of the xanthate group); ^{1}H-NMR (DMSO-d6/TMS): δ 1.20 (t, 3H, -C**H$_3$**), 4.40 (2H, -C**H$_2$**-), 4.50 (s, 2H, -C**H$_2$**-), 7.20-8.50 (m, 4H, **aryl protons**) 12.58 (broad s, 1H, D_2O exchangeable proton, –N**H**); LC-MS: m/z 281[M+H]$^{+}$.

Preparation of 9 from 8 and 2

A mixture of 2-(2-chloroacetylamino)benzamide (**8)** (2.12 gm, 10 mmol), **2** (10 mmol), K_2CO_3 (1.92 g, 15 mmol), TBAB (0.25g.) and DMF (10 mL) was stirred at RT for 2 h. After completion of the reaction, as monitored by TLC, the mixture was poured into ice-cold water (100 mL). The separated product was filtered, washed with water (2×25 mL) and dried to obtain **9a-b**.

9a: Yield = 2.30 g (74 %); M.p. = 113-115 ^{o}C (EtOH); IR (KBr) 3200-3100 cm^{-1} (NH & NH_2), 1700 cm^{-1} (C=O); ^{1}H NMR (DMSO-d_6) δ 4.44 (s, 2H, -C**H$_2$**-), 7.36-8.00 (m, 8H, **aryl protons**) 8.08 (b, s, 2H, D_2O, -N**H$_2$**) and 12.44 (b, s, 1H, D_2O, –N**H**); ^{13}C-NMR (DMSO-d_6/TMS) δ 38.5(CH_2), 110.2, 119.1, 123.2, 123.5, 124.4, 124.8, 126.9, 132.3, 137.0, 141.5, 151.9(aromatic carbons) and 172.1 (C=O); LC-MS m/z 327 $[M+H]^+$. Chemical Formula: $C_{16}H_{13}N_3O_3S$, Elemental Analysis: C, 58.70; H, 4.00; N, 12.84; O, 14.66; S, 9.80. Found: C, 58.72; H, 4.04; N, 12.82; O, 14.64; S, 9.80.

9b: Yield: 2.8 g (81 %); M.p. = 131-132 ^{o}C (Chloroform). IR (KBr): 3200-3100 cm^{-1} (very broad, N**H** & N**H$_2$**) , 1665 cm^{-1} (strong, C=O); ^{1}H NMR (DMSO-d_6): δ 4.36 (s, 2H, -C**H$_2$**-), 7.30-8.00 (m, 8H, **aryl protons**) 8.18 (broad s, 2H, D_2O exchangeable protons, -N**H$_2$**) and 12.43 (broad, singlet, 1H, D_2O; The ^{13}C-NMR spectrum (DMSO-d_6/TMS) The ^{13}C-NMR spectrum (DMSO-d_6/TMS) δ 38.3(CH_2), 110.2, 119.1, 123.2, 123.5, 124.4, 124.8, 126.9, 132.3, 137.0, 141.5, 151.9 (Aromatic Carbons) and 172.1(C=O). Chemical Formula: $C_{16}H_{13}N_3O_2S_2$, Elemental Analysis: C, 55.96, H, 3.82, N, 12.24, O, 9.32, S, 18.67. Found; C, 55.98, H, 3.84, N, 12.27, O, 9.35, S, 18.64; LC-MS: m/z 344 $[M+H]^+$.

Preparation of 5 from 9

A mixture of **9** (3.27 g, 10 mmol) and AcOH (20 mL) was refluxed for 3-4 h. After completion of the reaction, as monitored by TLC, the mixture was poured into ice-cold water (50 mL), and the pH of the mixture was adjusted to ≥ 7.0 with acetic acid. The separated solid was filtered, washed with water (2×25 mL) and dried to obtain **5a-b.** Pure **5a-b** (MeOH), identical in mp, mmp and TLC with that of the same product obtained in the route described above, i.e. **3**+**4** ⟶ **5**

5a: Yield = 2.25 g (72 %); M.p. = 190-192 ^{o}C (MeOH).

5b: Yield = 2.18 g (77 %); M.p. = 163-165 ^{o}C (MeOH).

Conclusion

The title compounds 2-((benzo[d]oxazol-2-ylthio)methyl)quinazolin-4(3H)-one (**4a**), 2-((benzo[d]oxazol-2-ylthio)methyl)quinazolin-4(3H)-one (**4b**) have been synthesized by three different routes. Of all the methodologies discussed, the condensation of **6** with **2** in MeOH as solvent using NaOH as base appears to be the better and efficient route for the product obtained, compare to the other two routes.

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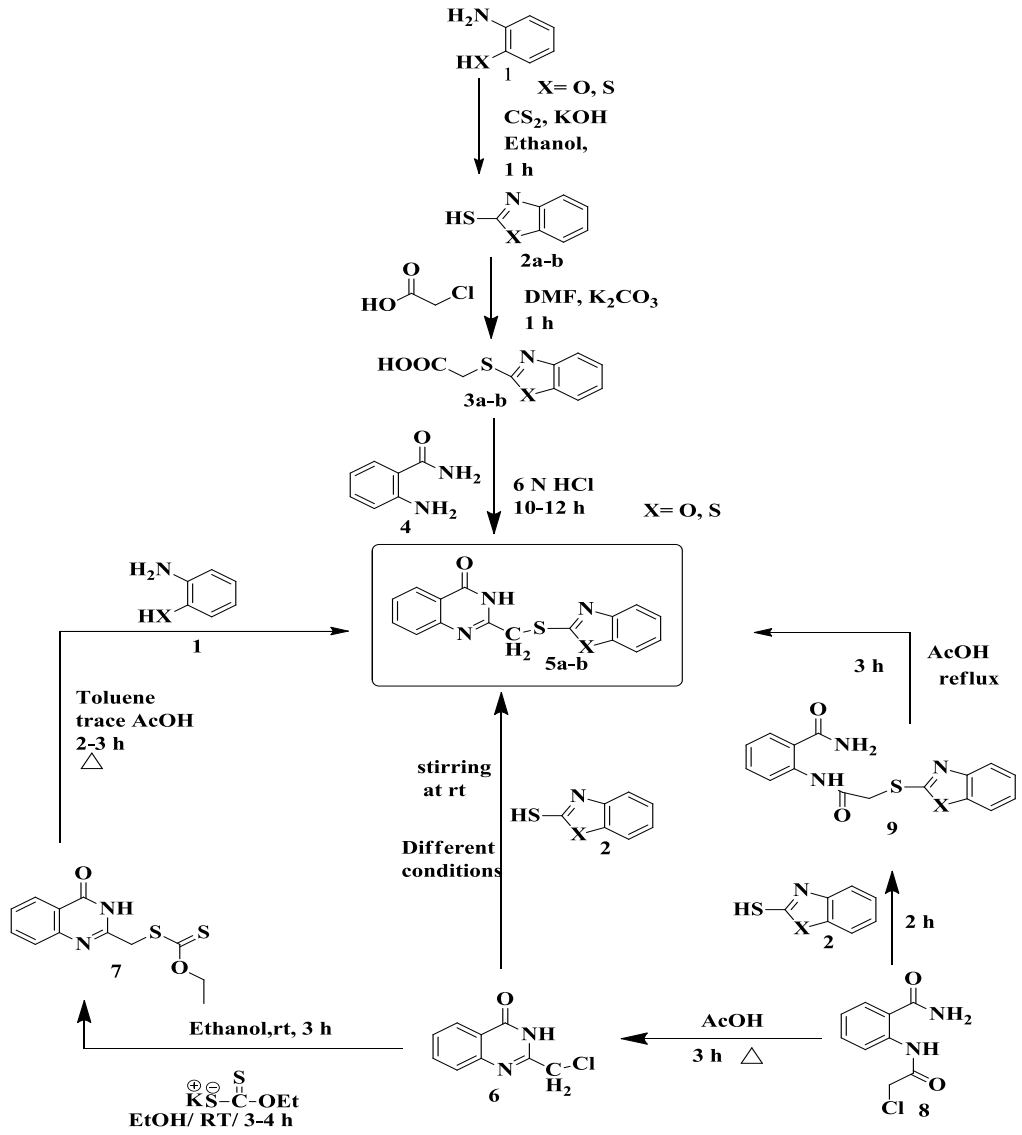
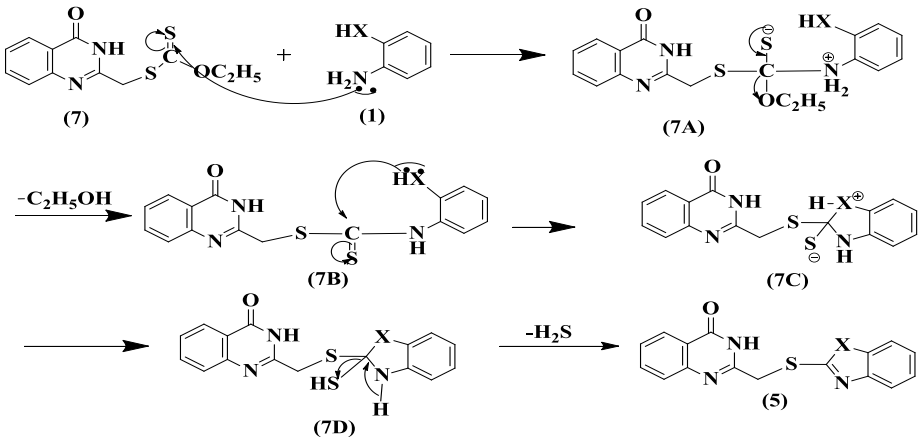
Table 1 Preparation of 5(a-b) from 6 and 2(a-b) by under different condition:

S.No.	Solvent used	Base used	Time (h)	Yield of 4(%)
1	Water	(5%) K_2CO_3 (5 mole %)	4	55
2	Water	(5%) NaOH (5 mole %)	4	60
3	Water	(5%) KOH (5 mole %)	4	60
4	PEG 600	____	3	70
5	**MeOH**	**NaOH (5 mole %)**	**3**	**90**
6	Acetonitrile	TEA (5 mole %)	3	80
7	DMF	K_2CO_3 (5 mole %)	2	80
8	MeOH	Piperidine (5 mole %)	3	75
9	MeOH	Pyridine (5 mole %)	3	60
10	DCM	TEA (5 mole %)	3	70
11	$CHCl_3$	TEA (5 mole %)	3	70



Scheme 1



Scheme 2