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Research Article

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Synthesis of 3-methyl-2-(((1-methyl-1*H*-benzo[d]imidazol-2-yl) sulfonyl) methyl)quinazolin-4(*3H*)-one

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ABSTRACT

*Condensation of 2-(chloromethyl)quinazolin-4(3H)-one **(1)** with benzo[d]imidazole-2-thiol **(2)** in acetone containing triethylamine as a base gave 2-(((1H-benzo[d]imidazol-2-yl)thio)methyl)quinazolin-4(3H)-one **(3)**. The later was treated with DMS (dimethyl sulphate) 1:2 ratio in DMF afforded 3-methyl-2-(((1-methyl-1H-benzo[d]imidazol-2-yl)thio)methyl)quinazolin-4(3H)-one **(4)**. The latter was reacted with H_2O_2 for 3 hr obtained 3-Methyl-2-(((1-methyl-1H-benzo[d]imidazol-2-yl)sulfonyl)methyl)quinazolin-4(3H)-one **(5)**. **5** could also be prepared by treating **3** with H_2O_2 followed by reaction with DMS in 1:2 ratios in DMF for 2 hr. The structures of all the new compounds synthesized in the work have been established on the basis of their spectroscopic data.*

Keywords: 2-Chloromethylquinazolin-4(3*H*)-one, Triethylamine, 2-thiobenzimadazole, H_2O_2

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] etc. 2-Thioquinazolin-4(3*H*)ones possess good analgesic activities[6]. 2-Heterylquinazolin-4(3*H*)-ones exhibit a wide range of pharmacological properties[8] such as good antimicrobial activity against different species of gram-positive bacteria[9], gram-negative bacteria[10], 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].

In view of these observations and in continuation of our earlier [24, 25] work on quinazolin-4(3*H*)-ones it was considered worthwhile to study the reaction of **1** with heterocyclic thiols and subsequent chemical modifications of the condensation products as new chemical entities with potential biological activities.

EXPERIMENTAL SECTION

General Conditions: Melting points are uncorrected and were determined in open capillary tubes in sulphuric acid bath. TLC was performed on silica gel-G and spotting was done using iodine or UV-light. IR spectra were recorded with Perkin-Elmer 1000 instrument in KBr phase, ^{1}H-NMR on VARIAN 400 MHz instrument and Mass spectra on Agilent-LC-MS instrument giving only $M^{+\cdot}$ values using Q+1or Q-1 mode.

Preparation of 3 from 1 and 2

A mixture of **1** (5 mM), **2** (10 mM) in acetone (25 mL), triethyl amine as a base (5 mM) and was stirred at RT for 3-4 hr. After completion of the reaction, as monitored by TLC, the mixture was poured into ice-cold water. The separated solid was filtered, washed with water, dried. **3** Yield = 2.80 g (90 %); M.P. 164-168 $^{\circ}$C(MeOH); IR (KBr): 3200-3100 cm^{-1} (very broad, two –NH-), 1650 cm^{-1} (strong, sharp, C=O of the amide carbonyl group); ^{1}H-NMR (DMSO-d_6/TMS): δ 4.35 (s, 2H, -C**H$_2$**-), 7.14-8.11 (m, 8H, **aryl protons**) and at 12.67 (br, s, 2H, D_2O exchangeable protons 2×–N**H**-); ^{13}C-NMR spectrum (DMSO-d_6/TMS) δ 34.83, 114.05, 121.11, 121.67, 125.85, 126.63, 126.89, 134.44, 139.49, 148.40, 149.75, 153.95, 161.67. LC-MS: *m/z* 309 [M+H] $^{+.}$

Preparation of 4 from 3

A mixture of **3** (10 mM), K_2CO_3 (10 mM) TBAB (0.125 g) and DMF (25 mL) was stirred at RT for 20 min. and was added alkylating agent i.e. dimethyl sulphate (DMS) (11 mM) and the mixture stirred at RT for 2 hr. At the end of this period, the reaction mixture was poured into ice-water (100 mL) and stirred for another 30 min. The separated solid was filtered, washed with water (10 mL) and dried to obtain crude product **9**. Yield : 2.45 g(72 %) ; M.P. 145-135 $^{\circ}$C; IR (KBr): 3200-3000 cm^{-1} (very broad, two –NH-), 1660 cm^{-1} (strong, sharp, C=O of the amide carbonyl group); ^{1}H-NMR (DMSO-d_6/TMS): δ 3.51 (s, 3H, -C**H$_3$**), 3.97 (s, 3H, -C**H$_3$**), 5.4 (s, 1H, -C**H$_2$**-), 7.2-8.00 (m, 8H, **aryl protons**); LC-MS : *m/z* 337 [M+H] $^{+.}$

Preparation of 5 from 4: To a suspension of **4** (10 Mm) in acetic acid (20 mL) was added H_2O_2 (30%) (2 mL) drop-wise at RT for 10 min. After completion of addition, the mixture was allowed to stirred at RT for 7 hr. At the end of the reaction as monitored by TLC, the mixture was diluted with ice-water (50 mL). The separated solid was filtered, washed with water (10 mL) and dried to obtain crude **5.**

Yield : 2.4 g (65 %); M.P. 155-158 $^{\circ}$C; IR (KBr): 3200-3000 cm^{-1} (very broad, two –NH-), 1660 cm^{-1} (strong, sharp, C=O of the amide carbonyl group); ^{1}H-NMR (DMSO-d_6/TMS): δ 3.51 (s, 3H, -C**H$_3$**), 3.97 (s, 3H, -C**H$_3$**), 5.4 (s, 1H, -C**H$_2$**-), 7.2-8.00 (m, 8H, **aryl protons**); LCMS : m/z 369 [M+H].

Preparation of 6 from 3

To a suspension of **3** (10 mM) in acetic acid (20 mL) was added H_2O_2 (30%) (2 mL) drop wise at RT for 10 min. After completion of addition, the mixture was stirred at RT for 7 hr. The reaction was monitored by TLC. After completion of the reaction, the mixture was diluted with ice-water (50 mL). The separated solid was filtered, washed with water and dried to obtain crude **6.** Yield : 1.85 g (55%); M.P. 198-200 $^{\circ}$C; IR (KBr): 3200-3000 cm^{-1} (very broad, two –NH-), 1660 cm^{-1} (strong, sharp, C=O of the amide carbonyl group) ; ^{1}H-NMR (DMSO-d_6/TMS): δ 3.51 (s, 3H, -C**H$_3$**), 3.97 (s, 3H, -C**H$_3$**), 5.4 (s, 1H, -C**H$_2$**-), 7.2-8.00 (m, 8H, **aryl protons**) and at 12.85 (br, s, 2H, D_2O exchangeable protons 2×–N**H**-); LC-MS : *m/z* 341 [M+H] $^{+.}$

Preparation of 5 from 6 (Alternative Method)

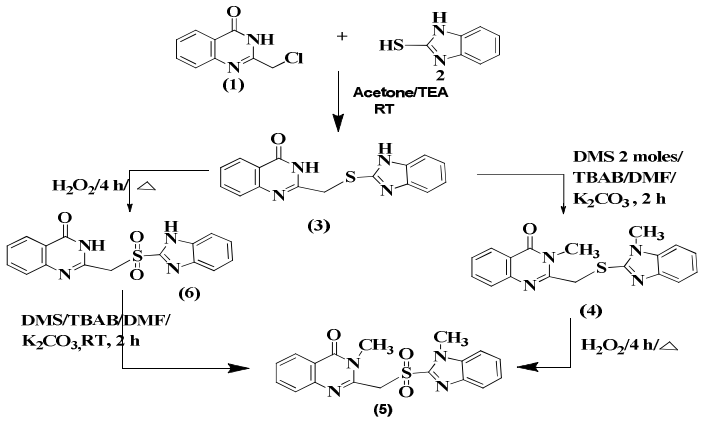
A mixture of **6** (10 mM), K_2CO_3, TBAB and DMF (20 mL) was stirred at RT for 20 min. and added alkylating agent (i.e. DMS) (11 mM) and the mixture stirred at RT for 2 hr. At the end of this period, the reaction mixture was poured into ice-water (100 mL) and stirred for another 30 min. The separated solid was filtered, washed with water (2×10 mL) and dried to obtain the crude product **5**. **5** identical in m.p., m.m.p., TLC and IR with that of the same product obtained in the route described above, (i.e. **3** ⟶ 4 ⟶ **5**).

RESULTS AND DISCUSSION

Condensation of 2-(chloromethyl)quinazolin-4(3*H*)-one **(1)** with 1*H*-benzo[d]imidazole-2-thiol **(2)** in acetone containing triethylamine as a base at RT for 2 hr gave a product which has been characterized as 2-(((1*H*-benzo[d]imidazol-2-yl)thio)methyl)quinazolin-4(3*H*)-one (**3**). The structure of **3** was established on the basis of its spectral and analytical data. Thus, its IR (KBr) showed a very broad band in the region 3400-3200 cm^{-1} due to two –NH- stretching vibration and a very strong, sharp peak at 1650 cm^{-1} due to the amide carbonyl group. Its ^{1}H NMR (DMSO-d_6) spectrum showed signals at δ 3.22 (s, 2H, -C**H$_2$**-), 7.14-8.11 (m, 8H, **aryl protons**) and at 12.65 (br, s, 2H, D_2O exchangeable protons 2×–N**H**-). Its ^{13}C-NMR spectrum (DMSO-d_6/TMS) showed signals at δ 34.83, 114.05, 121.11, 121.67, 125.85, 126.63, 126.89, 134.44, 139.49, 148.40, 149.75, 153.95, and 161.67. Its LC-MS spectrum showed the molecular ion peak at 309 corresponding to a molecular mass of 308 when recorded in the Q+1 mode.

The **3** was treated with dimethyl sulfate in DMF containing K_2CO_3 and TBAB at RT for 3 hr resulted 3-methyl-2-(1-methyl-1*H*-benzoimidazol-2-ylsulfanylmethylquinazolin-4(*3H*)-one (**4**). Whose structure thus, its IR (KBr) spectrum showed a sharp peak at ≈1680 cm^{-1} due to carbonyl group as diagnostic absorption. Its ^{1}H-NMR spectrum (DMSO d_6/TMS) showed signals at δ 3.51 (s, 3H, -C**H**$_3$), 3.97 (s, 3H, -C**H**$_3$), 5.4 (s, 2H, -C**H**$_2$), 7.2-8.00 (m, 8H, **aryl protons**). Its Mass spectrum, when recorded in the CI method, showed the molecular ion peak at 337 corresponding to a molecular mass of 336, when recorded in the Q+1 mode.

4 when reacted with hydrogen peroxide in excess at RT for 4-5 hr, gave 3-methyl-2-(((1-methyl-1*H*-benzo[d]imidazol-2-yl)sulfonyl)methyl)quinazolin-4(3*H*)-one(**5).** The structure of **5** was established on the basis of its spectral and analytical data. Thus, its IR (KBr) absence of absorption in the region 3200-3100 cm^{-1} absence –NH- stretching vibration and a very strong, sharp peak at 1660 cm^{-1} due to the amide carbonyl group. Its ^{1}H NMR (DMSO-d_6) showed signals at δ 3.51 (s, 3H, -C**H**$_3$), 3.97 (s, 3H, -C**H**$_3$), 5.4 (s, 1H, -C**H**$_2$), 7.2-8.00 (m, 8H, **aryl protons**). Its Mass spectrum, when recorded in the CI method, showed the molecular ion peak at 369 corresponding to a molecular mass of 368 when recorded in the Q+1 mode.



Scheme 1

In an alternative method, **5** could also be synthesized, treatment of **3** with H_2O_2 in acetic acid at RT for 7hr gave a product, which has been characterized as 2-[1-(1H-benzoimidazol-2-yl)ethanesulfonyl]-*3H*-quinazolin-4-one (**6**). Thus, its IR (KBr) showed a very broad band in the region 3200-3100 cm^{-1} due to the two –NH- stretching vibrations a sharp, strong peak at 1670 cm^{-1} due to the carbonyl group as diagnostic absorptions. Its ^{1}H NMR (DMSO-d_6) showed signals at δ 5.4 (s, 2H, -C**H**$_2$), 7.2-8.00 (m, 8H, **aryl protons**) and at 12.85 (br, s, 2H, D_2O exchangeable protons 2×–N**H**-). Its LC-MS spectrum showed the molecular ion peak at 355 corresponding to a molecular mass of 354 when recorded in the Q+1 mode.

Reaction of **6** with dimethyl sulfate in 1:2 ratio in DMF in the presence of K_2CO_3 as base and TBAB as phase transfer catalyst at RT for 2hr, gave 3-methyl-2-[1-(1-methyl-1*H*-benzoimidazol-2-yl)ethanesulfonyl]quinazolin-4(*3H*)-one (**5**). **5** identical in m.p., m.m.p., TLC and IR with that of the same product obtained in the route described above, (i.e. **6** ⟶ **5**). All the reactions described in this paper are neatly depicted in **Scheme 1**

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