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# A Green and Facile Synthesis of 2-Alkylsulfanyl-3*H*-quinazolin-4-one

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Reaction of 2-thioquinazolinone (**1**) with various alkylating agents like dimethyl sulphate, diethyl sulphate and benzyl chloride in the presence of $K_2CO_3$ as a mild base, by a simple physical grinding, microwave irradiation and PEG-600 under solvent-free conditions for 10-15 min at room temperature, followed by processing, gave respectively 2-methylsulfanyl-3*H*-quinazolin-4-one (**2a**, *i.e.*, R = $CH_3$), 2-ethylsulfanyl-3*H*-quinazolin-4-one (**2b**, *i.e.*, R = $C_2H_5$) and 2-benzyl sulfanyl-3*H*-quinazolin-4-one (**2c**, *i.e.*, R = $PhCH_2Cl$). It appears from this study that green syntheses such as solid phase synthesis (physical grinding) and microwave irradiation gives better yields, quality and in less reaction time the products over conventional methods involving green solvents like ethanol, PEG-600 *etc*. The entire sequences of reactions have been carried out using eco-friendly solvents and green conditions.

**Key Words: 2-Thioquinazolinone, Alkylating agent (DMS/DES/$PhCH_2Cl$), PEG-600, Ethanol, $K_2CO_3$, M.W.**

## 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 antiinflammatory[1,2], anticonvulsant[3], hypotensive[4] and antimalarial[5] types. 2-Thioquinazolinones possess good analgesic activities[6]. 2-Substituted quinazolin-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], pathogenic fungi[11,12], antitubercular activity[13,14] and antitumor chemotherapeutic agent[15,16].

## EXPERIMENTAL

All the reagents used in this work were obtained from commercial suppliers. Solvents were freshly distilled before being used. Melting points were determined using a Buchi melting point B-545 apparatus and are uncorrected. TLC analyses were done on glass plates coated with silica gel GF-254 and spotting was done using iodine/UV lamp. IR spectra were recorded on a Perkin-Elmer model 446 instrument in KBr phase. $^1$H NMR were recorded in $CDCl_3$/DMSO using 400 MHz Varian Gemini spectrometer and mass spectra were recorded on a LC-MS spectrometer, model HP-5989A. Experiments under microwave irradiation were carried out by using the commercially available CEM discover microwave reactor. Elemental analyses were performed by Varian 3LV analyzer series CHN analyzer.

### Preparation of 2-alkylsulfanyl-3*H*-quinazolin-4-one (2) from 2-thioquinazolinone (1)

**i) In solid phase:** A mixture of 2-thioquinazolinone (**1**) (1.78 g, 10 mM), $K_2CO_3$ (2.76 gms, 20 mM) and alkylating agent (10 mM) were ground together for about 10-15 min in a mortar and pestle at room temperature to obtain a homogeneous mixture. The latter was then treated with ice-cold water (*ca.* 30-40 mL). The separated solid was filtered, washed with water (2 × 10 mL) and dried to obtain crude 2-alkylsulfanyl-3*H*-quinazolin-4-one (**2**). The crude product was recrystallized from ethanol to obtain pure **2** (**a-c**) (Table-1).

**ii) In solution phase: 1) In PEG-600:** A mixture of **1** (1.78 g, 10 mM), alkylating agent (10 mM) and PEG-600 (20 mL) was stirred at room temperature for 2 h. At the end of this period, the mixture was poured into ice-cold water (*ca.* 50 mL). The separated solid was filtered, washed with water (2 × 10 mL) and dried. The crude product was recrystallized from ethanol to obtain pure **2** (**a-c**) (Table-1).

**2) In ethanol:** A mixture of **1** (1.78 g, 10 mM), $K_2CO_3$ (2.76 g, 20 mM) ethanol (50 mL) and the alkylating agent (10 mM) was stirred at RT for 2 h. The progress of reaction was monitored on TLC for the disappearance of **1**. After the completion of the reaction (*ca.* 2 h), the excess ethanol was rotary evaporated and the residual mixture poured into ice-cold water (2 × 20 mL). The separated solid was filtered, washed with water (20 mL) and dried. The crude product was recrystallized from ethanol to obtain pure **2** (**a-c**) (Table-1).

TABLE-1
PREPARATION OF **2** FROM **1** UNDER DIFFERENT CONDITIONS

| S. No. | Substrate | Reagent | Product | Solid phase | | | Green solvent (solution phase) | | | Microwave irradiation | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | PEG-600 | | Ethanol | | | | |
| | | | | Time (min) | Temp. | Yield* (%) | Time (min) | Yield* (%) | Time (min) | Yield * (%) | Time (min) | Temp/ Wattage | Yield* (%) |
| 1 | 1 | DMS | **2a** | 10-15 | RT | 80 | 130 | 65 | 130 | 70 | 5 | RT/450W | 82 |
| | | DES | **2b** | 10-15 | RT | 90 | 130 | 60 | 130 | 60 | 5 | RT/450W | 80 |
| | | Ph-$CH_2$-Cl | **2c** | 10-15 | RT | 90 | 140 | 70 | 140 | 60 | 5 | RT/450W | 73 |

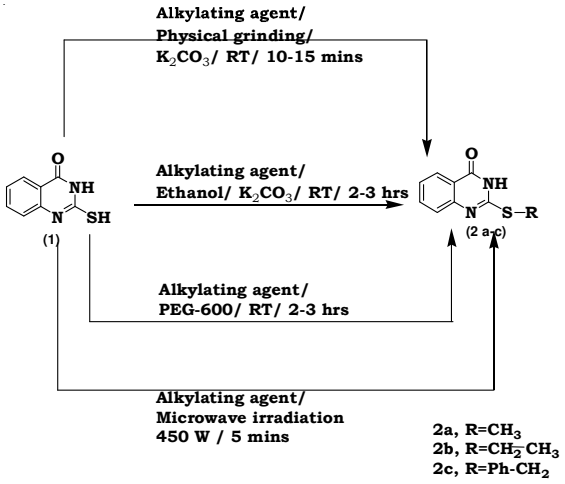
m.p. of **2a** 220-222 ºC. (Lit.[17] m.p. 224-225 ºC). m.p. of **2b** 202-204 ºC. (Lit.[18] m.p. 205-207 ºC); m.p. of **2c** 176-177 ºC. (Lit.[19] m.p. 178-180 ºC).
*Yields refer to processed crude products, RT = Room temperature.

**Under microwave irradiating conditions:** Mixture of **1** (1.78 g, 10 mM) and alkylating agent (10 mM) was taken in a 10 mL CEM-reaction tube sealed by rubber stopper and subjected to microwave irradiation for 5 min at 130 ºC in the commercial micro-wave reactor. After that, the tube was cooled and the completion of reaction was checked by TLC then poured into ice-cold water (2 × 20 mL). The separated solid was filtered, washed with water (2 × 10 mL) and dried. The crude product was recrystallized from ethanol to obtain pure **2** (**a-c**) (Table-1).

## RESULTS AND DISCUSSION

Reaction of **1** with various alkylating agents like dimethyl sulphate, diethyl sulphate and benzyl chloride ($PhCH_2Cl$) in the presence of $K_2CO_3$ as a mild base, by a simple physical grinding of the reaction mixture in a mortar and pestle under solvent-free conditions for 10-15 min at room temperature, followed by processing, gave respectively 2-methylsulfanyl-3*H*-quinazolin-4-one (**2a**, *i.e.*, R = $CH_3$), 2-ethylsulfanyl-3*H*-quinazolin-4-one (**2b**, *i.e.*, R = $C_2H_5$) and 2-benzyl sulfanyl-3*H*-quinazolin-4-one (**2c**, *i.e.*, R = $PhCH_2Cl$), as the products identical with the one reported in the earlier methods[17-19] in all respects (m.p. m.m.p and co-tlc analysis).

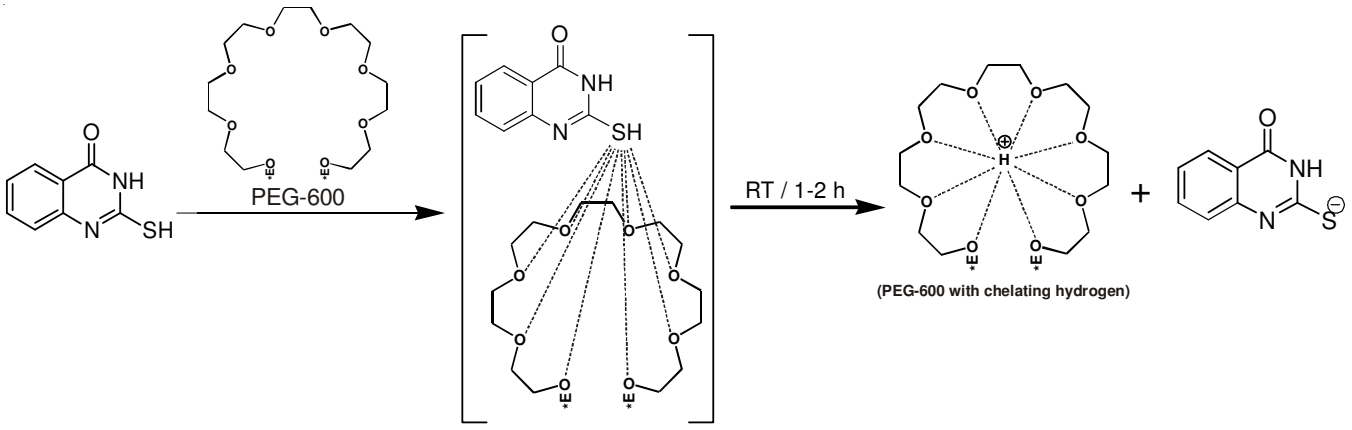
The reaction was also carried out in ethanol as a solvent. Thus, treatment of **1**, independently, with each of dimethyl sulphate, diethyl sulphate and benzyl chloride ($PhCH_2Cl$) in ethanol at room temperature for 2 h $K_2CO_3$ as a base, followed by simple processing, gave respectively, **2a** (*i.e.*, **2**, R = $CH_3$), **2b** (*i.e.*, **2**, R = $C_2H_5$) and **2c** (*i.e.*, **2**, R = $PhCH_2$) identical with the same products obtained above (**Scheme-I**).

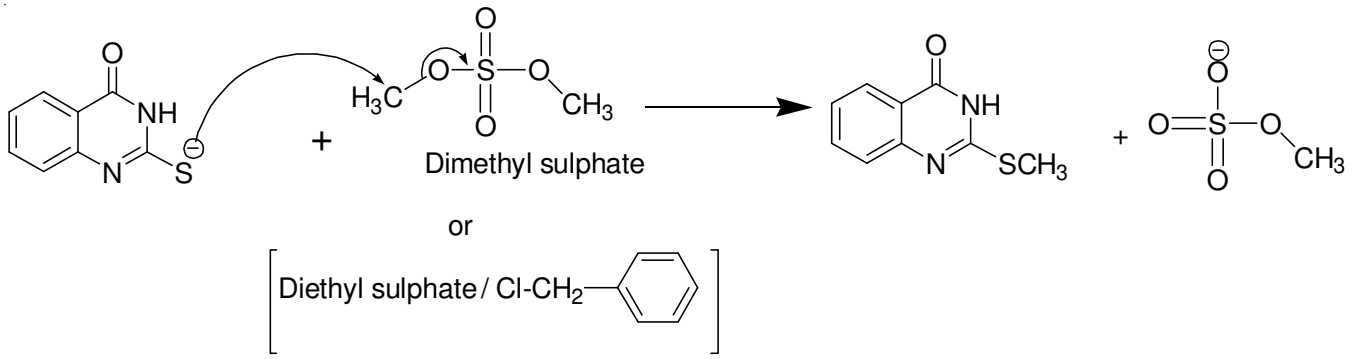



**Scheme-I**

The reaction was also carried out in PEG-600 as a solvent. Thus, treatment of **1**, independently, with each of dimethyl sulphate, diethyl sulphate and benzyl chloride ($PhCH_2Cl$) in PEG-600 at room temperature for 2 h without the use of any base, followed by simple processing, gave respectively, **2a** (*i.e.*, **2**, R = $CH_3$), **2b** (*i.e.*, **2**, R = $C_2H_5$) and **2c** (*i.e.*, **2**, R = $PhCH_2$) identical with the same products obtained above (**Scheme-I**). It is obvious from the above results that PEG-600 is a very efficient solvent for the alkylation of 1 resulting in the formation of **2**(**a-c**) respectively. Mechanistic explanation[20] of these results is that, probably PEG-600 dissolves the substrates **1** and the reagent (*i.e.* the alkylting agent, dimethyl sulfate, diethyl sulfate, *etc*.), bringing them together thereby providing an effective means for chemical reaction to occur. Further, PEG-600 is

**Plausible mechanism:**






able to extract the hydrogen from the -SH of quinazolinone and is able to retain it in its claws by chelation through several lone pairs of electrons in its oxygen containing chain. The sulphanyl anion from the substrate **1** then attacks the positively polarized methyl carbon of the alkylating agent bringing about product (**2**) formation. This role of PEG-600 is very similar to that of the crown ethers or that of the proton sponge (*i.e.* 1,8-dimethylaminonaphthalene). The latter acts as a very strong base due to its ability to extract hydrogen from an acidic substrate and then retain it by chelation through lone pair of electrons on the two nitrogen atoms of the two amino groups (**Scheme-I**).

**2(a-c)** could also be prepared by an alternative method. Thus, **1** on reaction independently, with each of dimethyl sulphate, diethyl sulphate and benzyl chloride ($PhCH_2Cl$) under microwave irradiation conditions for 5-8 min and subsequent processing, gave respectively **2a** (*i.e.*, **2**, R = $CH_3$), **2b** (*i.e.*, **2**, R = $C_2H_5$) and **2c** (*i.e.*, **2**, R = $PhCH_2$) identical with the products obtained earlier above.

## Conclusion

In conclusion, green and simple syntheses of 2-alkylsulfanyl-3*H*-quinazolin-4-one (**2a-c**) from **1** are described. It appears from this study that Green syntheses such as solid phase synthesis (physical grinding) and micro wave irradiation gives better yields, quality and in less reaction time the products over conventional methods involving green solvents like ethanol, PEG-600 *etc*. The entire sequence of reactions shown in **Scheme-I** have been carried out using eco-friendly solvents and green conditions.

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