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A FACILE AND CONVENIENT METHOD TO THE ONE-POT SYNTHESIS OF 2-MERCAPTO-4(3*H*)-QUINAZOLINONES

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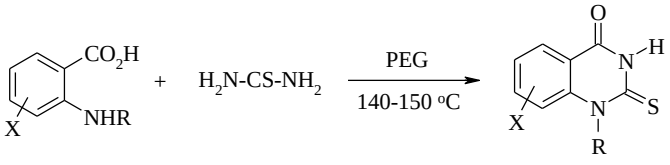
Abstract – A facile and convenient method to the one-pot synthesis of 2-mercapto-4(3*H*)-quinazolinones is described from the reaction of anthranilic acid derivatives with thiourea in PEG.

2-Mercapto-4(3*H*)-quinazolinone derivatives represent one of the most active classes of heterocycles possessing a wide spectrum of industrial[1] and biological activities.[2-5] Due to their diverse and remarkable applications, considerable attention has been focused on their synthesis.[3,6] The simplest and most accessible method has proven to be the one based on the reaction of anthranilic acid or its functional derivatives with a source of NH and thiocarbonyl such as thiocyanate salts and isothiocyanates.[6a,6c,6f,6g] Although some of these synthesis methods are very useful, most of them are associated with one or the other limitations, such as involving two or more steps, use of very toxic chemicals, employment of harsh reaction conditions, low reaction yields and moreover the low availability of starting materials. Certainly, exploitation of simple reagents with good reaction yields and development of convenient methods to synthesize or to modify such compounds is a worthwhile effort in heterocycles synthesis, and could be of interest.

Here, we wish to report a convenient and simple procedure for the one-pot synthesis of 2-mercapto-4(3*H*)-quinazolinones **2** by direct cyclocondensation reaction of anthranilic acid derivatives **1** with thiourea in polyethyleneglycol (PEG). The reaction proceeds in neutral media and without use of any catalyst (Scheme 1).

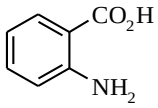
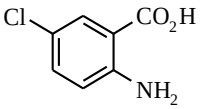
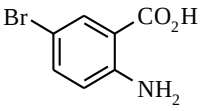
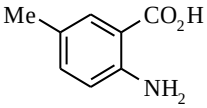
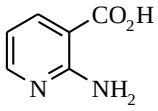
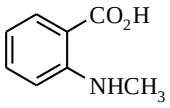


1 **2**

Scheme 1

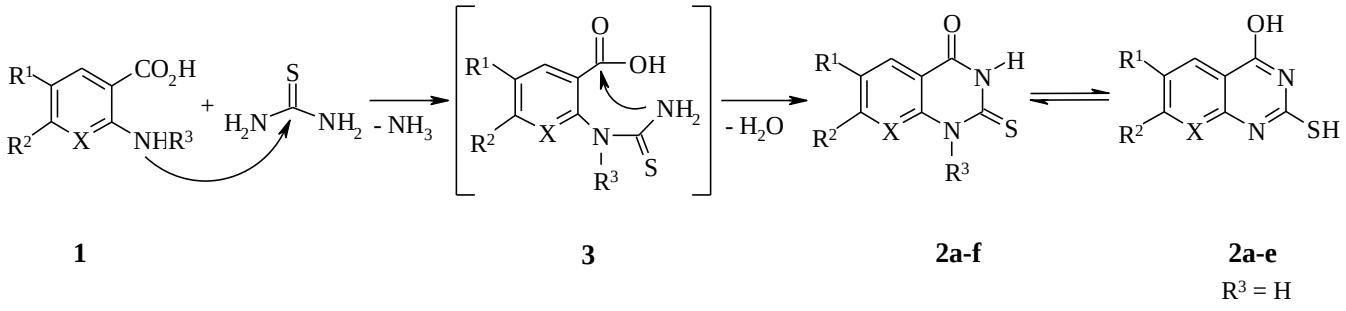
The reaction conditions are mild and the reaction procedure is simple. Results are shown in Table 1.

Table 1. Reaction of anthranilic acid derivatives **1** with thiourea in PEG

	1	Time/h	Yield **2** /% [a,b]	Mp/°C (lit.)
a		5.5	80	292-295 (294-296[6c])
b		4.5	72	351-354 (355[7])
c		4.5	74	321-324 (323-325[6b])
d		4	82	287-289 (288-290[6b])
e		4	70	275-278 (280[8])
f		6.5	30	252-255 (255-257[6c])

[a] In all cases, the products were identified and characterized by comparison of their physical and spectral data with those of authentic samples. [b] Isolated yield.

The proposed mechanism is shown in Scheme 2. It is reasonable to assume that **2** results from an initial addition of the amine group of **1** to thiourea and subsequent cyclocondensation of the unstable intermediate **3** under the same reaction conditions.



Scheme 2

As it is shown in Table 1, the yield of **2f** is low, probably because of some steric of nucleophile. Also, it cannot tautomerise to the stable aromatic structure.

The reactions were carried out in PEG as an excellent green solvent[9] with high boiling point. It easily

dissolves the polar anthranilic acid derivatives and thiourea. Also, it is miscible with water; therefore, it is simple to remove the solvent and the residual thiourea in work-up process by washing of the reaction mixture in water. In similar conditions, the reactions do not proceed in DMF and in EtOH.

In conclusion, the present procedure develops a simple and convenient method for the one-pot synthesis of 2-mercapto-4(3*H*)-quinazolinones in neutral media and without need to use any catalyst. Also, this procedure provides good yields of products with easy work-up of the reaction mixtures.

ACKNOWLEDGEMENTS

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10. *General reaction procedure:* In a 25 mL round flask a mixture of anthranilic acids **1a-f** (5 mmol), 0.38 g (5 mmol) of thiourea, and 1 mL PEG was heated at 140-150 ^{o}C for the times as indicated in Table 1. The reaction mixture was cold to rt; then, H_2O (5 mL) was added and mixed with the contents and decanted (three times). The raw products were washed with 10% aqueous $NaHCO_3$ to remove the residual of anthranilic acid derivatives. The products collected and dried first in air then in oven (100 ^{o}C). They may be recrystallized from EtOH or EtOH/EtOAc, if needed.