Heterocyclic Compounds; IX. A Facile Synthesis of Methaqualone and Analogs[1]

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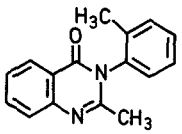
The biological activity of quinazoline derivatives in general and CNS (central nervous system) activity of methaqualone (**1**) and its analogs in particular have resulted in the development of many different syntheses of this class of compounds[2]. We wish to report here a new and facile synthesis of **1** and its variously substituted analogs.



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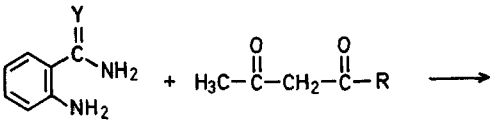
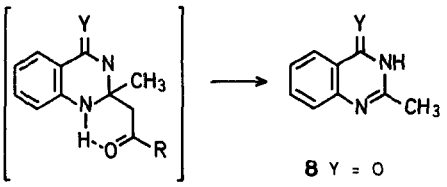
β-Diketones, in particular acetylacetone, have been used in the synthesis of substituted pyridines[3], pyrazoles[4,5], pyrimidines[6], pyrazolopyrimidines[7,8] and diazepines[9]. For example, Zvilichovsky[6] reported condensation between both keto groups of acetylacetone and alkoxyureas to produce 2-oxodihydropyrimidines in high yield. In the hope of preparing diazocines by an analogous reaction between acetylacetone and an *o*-aminoamide, such as **2**, we have further explored this reaction. The reaction of anthranilamide (**2a**) with acetylacetone (**3a**) in 6% ethanolic hydrogen chloride afforded in 2 min 2-methyl-4-quinazolone (**8**) in nearly quantitative yield. The identity of this compound was confirmed by a comparison of its m.p., I.R., N.M.R., and mass spectral fragmentation behaviour with an authentic sample[2]. The appearance of **8** in this reaction is surprising. However, its formation could be rationalized as proceeding through the loss of an acetone molecule from the intermediate 1,2-dihydroquinazolone (**4**) by a retro-aldol type elimination.



2a Y = O
b Y = S

3a R = CH_3
b R = C_6H_5



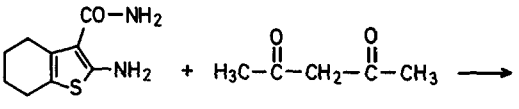
8 Y = O
9 Y = S

4 Y = O, R = CH_3
5 Y = S, R = CH_3
6 Y = O, R = C_6H_5
7 Y = Z, R = C_6H_5

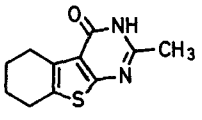
The high yield and the rapidity of this reaction is compatible with an intramolecular reaction. Written as a 6-centered intramolecular reaction, the elimination of acetone from **4** is reminiscent of the McLafferty rearrangement in mass spectroscopy[10], Norrish-type cleavage of ketones under ultraviolet irradiation[11], and a photoelimination reaction of *N*-heteroaromatic compounds[12].

This reaction is acid catalyzed and does not take place in neutral or basic media. Thus **2a** was recovered unchanged after an overnight reflux with **3a** in ethanol or toluene. Treatment of **2a** with **3a** in ethanol, benzene, toluene, or xylene using piperidine as the condensing agent under the conditions used for the synthesis of pyrazolopyrimidines[7] did not give any cyclized product; an almost quantitative amount of **2a** was recovered after the reaction. Alternatively, refluxing **2a** with **3a** for 2 h in benzene in presence of a catalytic amount of *p*-toluenesulfonic acid using a Dean-Stark water separator led to **8** in nearly quantitative yield.

Similar reaction of **3a** with thioanthranilamide (**2b**) and with 2-amino-3-carboxamido-4,5-tetramethylenethiophene (**10**) in hydrochloric acid/ethanol gave the known pyrimidine derivatives **9**[13] and **11**[14], respectively. Apparently in all these reactions the same type of intermediate is involved as postulated in the formation of **8**.



10 **3a**



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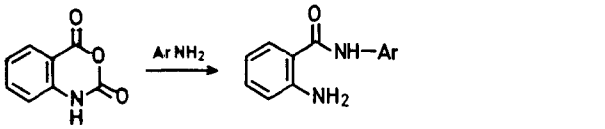
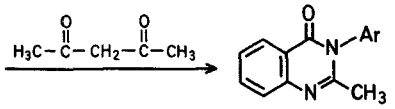
To ascertain the general applicability of this facile synthesis of quinazoline derivatives the reaction of benzoylacetone (**3b**) with *o*-aminoamides was investigated. It was found

that benzoylacetone (**3b**) reacted with **2a**, **2b**, and **10** in hydrochloric acid/ethanol solution under similar reaction conditions to give **8**, **9**, **11**, respectively. The formation of the same end products **8**, **9**, and **11** from **2a**, **2b**, and **10** using acetylacetone (**3a**) or benzoylacetone (**3b**) is noteworthy.

The usefulness of acetylacetone (**3a**) as a reagent for the facile synthesis of 2-methyl-4-quinazolones was utilized in developing a new one-pot synthesis of (**1**)[15]. It has been reported that isatoic anhydride (**12**) reacts with amines to form *o*-aminoamides (**13**)[16]. We have found that acetylacetone reacts with these suitably substituted aminoamides resulting in their cyclization to the 2-methyl-3-aryl-4-quinazolones (**1**). It was further noticed that the isolation of the *o*-aminoamides was not necessary and the quinazolone synthesis can be achieved as a one-pot reaction.



12 **13**



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Thus, when **12** and *o*-toluidine were refluxed together in xylene the aminoamide **13**, Ar = 2-H_3C—C_6H_4 was formed. The course of this condensation reaction was studied spectroscopically. The disappearance of the pronounced absorption peaks of isatoic anhydride (1740 and 1720 cm^{-1}) carbonyl groups and the appearance of peaks at 3450, 3350 (NH_2), and 1660 cm^{-1} (amide CO) was indicative of completion of this phase of the reaction. The isolation of the intermediate **13** was found unnecessary for the next phase in which cyclization to methaqualone (**1**) was accomplished by treatment with **3a**. This method appears to have general applicability for the synthesis of this category of compounds.

Melting points were determined on a Mel-Temp Apparatus. I.R. spectra were obtained on a Perkin-Elmer 247 Grating Spectrometer, ^{1}H-N.M.R. spectra in $CDCl_3$ or DMSO-d_6 solutions containing TMS as an internal standard were recorded on a Varian A-60 A spectrometer and mass spectra were obtained with a Hitachi RMU-7 spectrometer.

General Procedure for the Reaction of *o*-Aminoamides with Diketones:

Anthranilamide (0.01 mol) and acetylacetone (0.01 mol) are heated for 2–3 min in 6% ethanolic hydrogen chloride (10 ml). The reactants first form a homogeneous solution and then the product begins to precipitate. After cooling, the reaction mixture is diluted with ether and filtered. The precipitated product is recrystallized from dimethylformamide/ethanol.

The 2-methyl-4-quinazolone **8**[2] and its analogs **9**[13] and **11**[14] were identified by direct comparison with the known compounds.

Synthesis of 2-Methyl-3-(*N*-*o*-tolyl)-4-oxoquinazoline (1; Methaqualone):

Method A: A mixture of isatoic anhydride (1.6 g, 0.01 mol) and *o*-toluidine (1.1 g, 0.01 mol) is heated at 120° for 2 h. The reaction mixture after cooling is triturated with ether. The resulting solid is collected by suction and recrystallized to give **13** (Ar = 2-H_3C—C_6H_4); yield: 1.7 g (75%); m.p. 110° (dichloromethane/hexane).

A mixture of the above amide (0.5 g, 0.0025 mol), acetylacetone (0.39 g, 0.0025 mol) in ethanol (30 ml) containing a few drops of concentrated hydrochloric acid is refluxed for 1 h. On cooling the title compound separated as the hydrochloride; yield: 0.59 g, (85%), m.p. 235–237°; $M^{\oplus}$ at $m/e = 250$.

Method B: A mixture of isatoic anhydride (1.6 g) and *o*-toluidine (1.1 g) in toluene (200 ml) is refluxed for 2 h. Acetylacetone (0.5 g) containing a few drops of concentrated hydrochloric acid is then added and the refluxing is continued for an extra hour. Evaporation of the solvent gives the title compound which is purified as the hydrochloride; yield: 80%.

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