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# *t*-BUTYLATION OF QUINAZOLINE[1,2]

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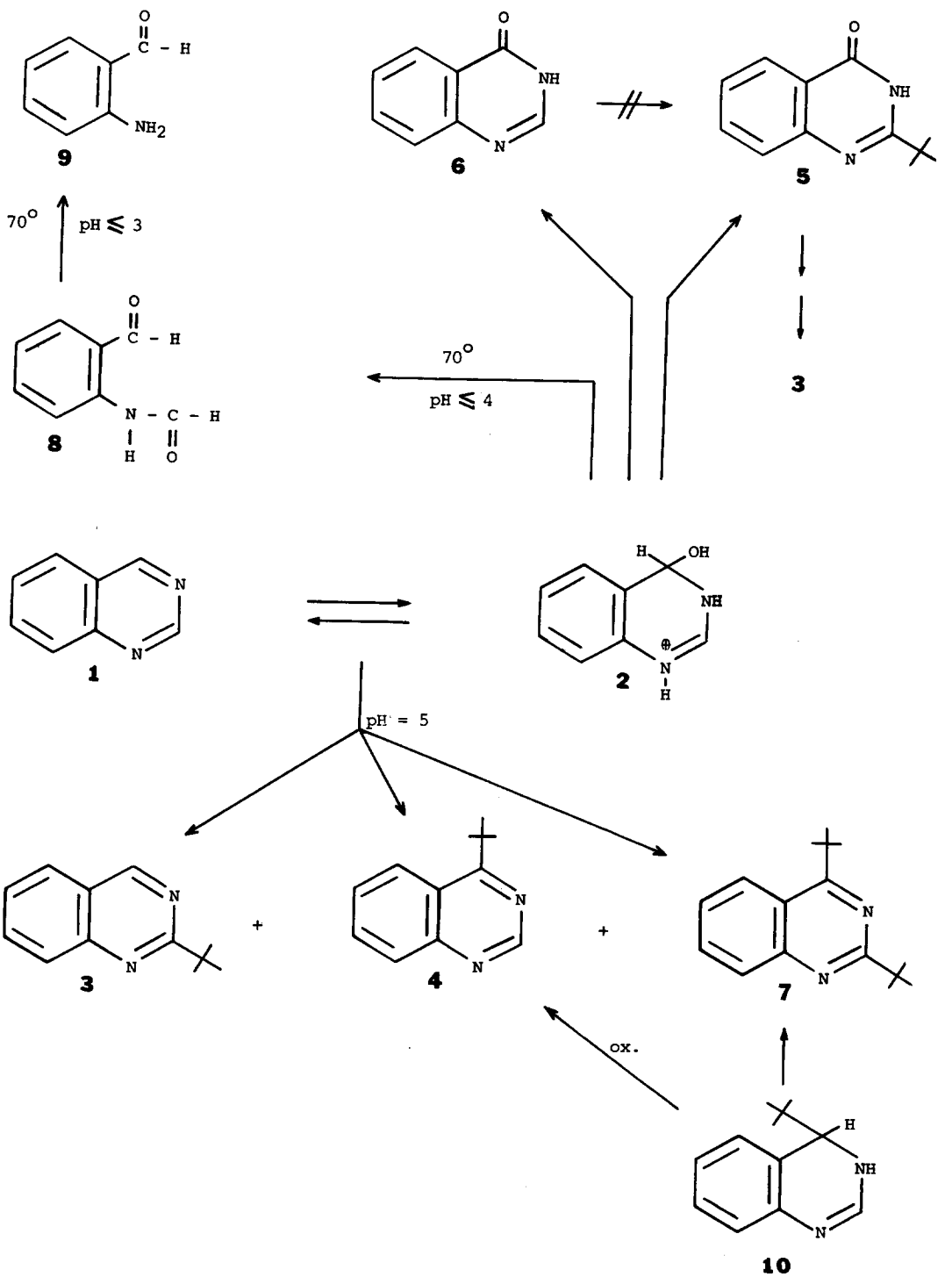
Various azaaromatics are smoothly converted into their alkyl derivatives on treatment with an oxidizing agent - carboxylic acid-silver nitrate system.[3] In our Laboratory we applied this method to the synthesis of alkyl pyrimidines[2] and found that substitution at position 4 is preferred to substitution at position 2. Our current interest in reactions of pteridine and substituted pteridines with nucleophiles induced us to investigate the *t*-butylation of these compounds, using as carboxylic acid pivalic acid, as oxidizing agent ammonium peroxydisulphate and as catalyst silver nitrate. However, we found that complicated product mixtures arise.

We therefore directed our attention to the *t*-butylation of the structurally related heterocycle, quinazoline, and the results of this investigation are reported in this paper.

Quite unlike pyrimidine, quinazoline (1) is mainly present as the cationic covalent hydrate (2) in an aqueous solution at pH = 3 ($pK_a$ = 3.51).[4] Therefore, on treatment of an aqueous solution of 1 with an excess of pivalic acid and ammonium peroxydisulphate, in the presence of a catalytic amount of silver nitrate at 40°C and at pH 1-0, not 2-*t*-butyl- (3) and/or 4-*t*-butylquinazoline (4), but 2-*t*-butyl-3,4-dihydro-4-oxoquinazoline (5) was formed quantitatively 3,4-Dihydro-4-oxoquinazoline (6) could not be detected in the reaction mixture. Since 6 was found to be inert for *t*-butylation, compound 5 must be formed *via* oxidation of the covalent hydrate of 3. Quinazoline can indeed be quantitatively converted into 6 under the same conditions, in the absence of pivalic acid.

In order to evaluate the influence of the pH on the course of the *t*-butylation, we studied the reaction under carefully controlled conditions. Since the pH of the solution gradually decreases as the reaction proceeds, due to i) the addition of the ammonium peroxydisulphate and ii) the liberation of hydronium ions, the use of a radiometer was necessary in order to maintain a preset pH during the experiment. We found that at pH > 6 no conversion of quinazoline into products occurs. Starting material was recovered quantitatively.


9
6
5
70°
pH ≤ 3
8
70°
pH ≤ 4
3
1
2
pH = 5
3
4
7
ox.
10

However, when quinazoline was reacted at 70°C and at pH = 5 for 2 hrs, it was almost completely converted into three products, identified as 2-*t*-butylquinazoline (3), 4-*t*-butylquinazoline (4) and 2,4-di-*t*-butylquinazoline (7), in a ratio of 4 : 3 : 2, respectively. No formation of a 3,4-dihydro-4-oxoquinazoline derivative is observed. Apparently at this pH the concentration of a covalent hydrate is too small to be of any importance to influence the course of the reaction. As yet 4 and 7 have not been described in the literature. Severe doubts on the existence of 4 as a stable species were reported. We found, however, that 4 is a stable compound, despite the suggested[6] steric interaction of the bulky 4-substituent and H-5.

Interestingly, the same reaction pattern is found at pH = 4, in spite of the presence of an increased amount of the covalently hydrated cation 2. At this pH value, however, caused by the elevated reaction temperature (70°C), fairly large amounts of products 8 and 9 were formed[5], probably due to acid-catalyzed hydrolysis of 1. GC-MS analysis shows that this reaction mixture contains further trace amounts of other di- and even tri-*t*-butyl substituted quinazolines of unidentified structure.

At pH = 3, 9 was found to be the main product. However, in addition to small amounts of 3, 4 and 7, a stable *t*-butyldihydroquinazoline (30%) appeared to be formed. This was identified as 4-*t*-butyl-3,4-dihydroquinazoline (10), as proved by comparison with an authentic specimen, previously prepared by the action of *t*-butyl magnesium chloride on 1.[6]
Compound 10 was reported, using various oxidizing agents, to give 1 instead of 4-*t*-butylquinazoline (4), by loss of the *t*-butyl group.[6] In our hands, however, 10 could easily be oxidized to 4 in an overall yield of 40% by an acetone solution of potassium permanganate. Quinazoline was formed as the sole by-product. Attempts to generate 10 in high yield by the *t*-butylation of 1 at pH = 2 failed, even at moderate temperature, due to the formation of appreciable quantities of 5. Compound 10, conveniently prepared by the action of *t*-butyllithium on 1 in ether at 5°C, was found to be quantitatively converted into 7, on treatment with an excess of alkylating reagent at pH = 5.
Since 5 can be converted into 3 in a high overall yield by a procedure involving replacement of the oxo group by a chloro atom, then hydrazinolysis of the chloro compound and oxidation of the hydrazino compound, the *t*-butyl quinazolines 3, 4 and 7 are now readily accessible in good yields.

At present we are establishing the interesting physical and chemical properties of these novel quinazolines. These data will be published elsewhere. The alkylation of the pteridines

is now under renewed investigation, as this approach would seem an attractive alternative for the laborious syntheses of this type of compound by the usual procedures.[7,8]

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Experimental

*4-t-butylquinazoline* (4). To 4-*t*-butyl-3,4-dihydroquinazoline[6] (1.5 g, 9.3 mmoles), dissolved in acetone (200 ml) was added $KMnO_4$ (2.0 g). After stirring for 16 hrs at room temperature, the excess of $KMnO_4$ was decomposed by the addition of 2-propanol. The reaction mixture was filtered and the solvents removed *in vacuo*. The residue was chromatographed on silica gel, eluent ethyl acetate, to yield a colourless liquid (0.63 g, 40%), b.p. 80°C/0.25 mm Hg. Prolonged elution afforded 0.42 g of quinazoline.(Found: C, 77.3; H, 7.5.$C_{12}H_{14}N_2$(186.25) requires C, 77.38; H, 7.58).

*2,4-di-t-butylquinazoline* (7). To a solution of 1.9 g (10 mmoles) of 4-*t*-butylquinazoline, 10.2 g (100 mmoles) of pivalic acid and 0.17 g (1.0 mmole) of $AgNO_3$ in 250 ml of water at 80°C was added a solution of 11.4 g (50 mmoles) of $(NH_4)_2S_2O_8$ in 150 ml of water over a period of 30 min. A pH value of 5.0 was maintained automatically during the addition. After stirring for 1 h the pH was raised to 8.0 by the addition of 2N NaOH. The cooled solution was extracted with $CHCl_3$ (250 ml), the extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The gum thus obtained was chromatographed on silica gel, eluent $CH_2Cl_2$, to yield a colourless liquid (1.7 g, 70%), b.p. 98°C/0.3 mm Hg.(Found: C, 79.2; H, 8.9. $C_{16}H_{22}N_2$(242.35) requires C, 79.29; H, 9.15).*2-t-butyl-3,4-dihydro-4-oxoquinazoline* (5). Amounts of up to 5 g of quinazoline, reacted under standard conditions as described in the literature[2] with pivalic acid, invariably yielded 2-*t*-butyl-3,4-dihydro-4-oxoquinazoline quantitatively. This compound was identified by comparison with an authentic specimen.[9]

References

1. Part LXXVI on Pyrimidines from this Laboratory. Previous paper E.A.Oostveen and H.C.van der Plas, Rec.Trav.chim., submitted.
2. H.C.van der Plas and A.Koudijs, Rec.Trav.chim. 97, 159 (1978).
3. F.Minisci, Topics in Current Chemistry, 62, 1 (1976).
4. W.L.F.Armarego, J.Chem.Soc., 1962, 561.
5. A.Albert and H.Yamamoto, J.Chem.Soc.(B), 1966, 956.
6. W.L.F.Armarego and J.I.C.Smith, J.Chem.Soc., 1965, 5360.
7. J.P.Geerts, A.Nagel and H.C.van der Plas, Org.Magn.Reson., 8, 607 (1976).
8. G.K.Helkamp and S.Kondo, Biochim.Biophys.Acta, 157, 242 (1968).
9. F.Piozzi, M.Dubini and M.Cecere, Gazz.Chim.Ital., 89, 2342 (1959).

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