The synthesis of substituted 2-aryl 4(3*H*)-quinazolinones using $NaHSO_3$/DMA. Steric effect upon the cyclisation-dehydrogenation step

J. Chem. Research (S), 2000, 258–259
J. Chem. Research (M), 2000, 0716–0726

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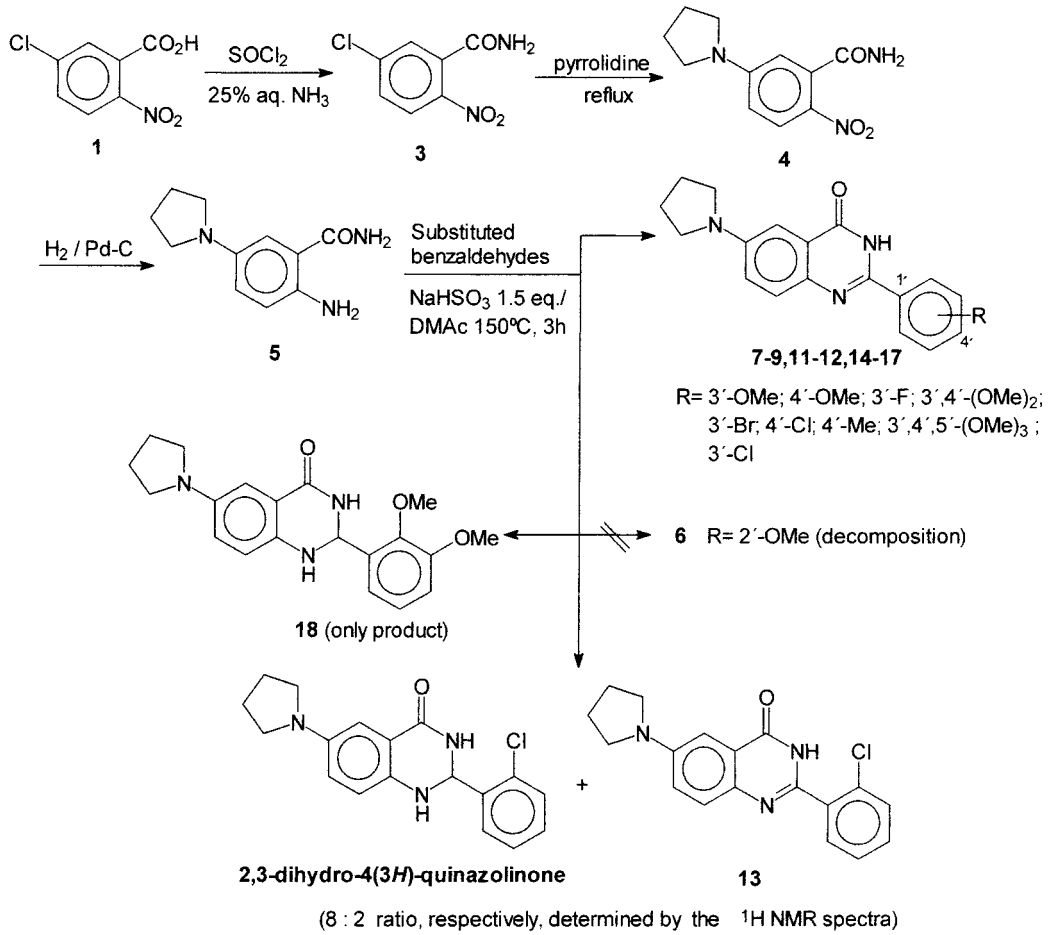
A number of 2-aryl substituted 6-pyrrolidino-4(*3H*)-quinazolinones are reported. They were synthesised in four steps starting from commercially available 5-chloro-2-nitrobenzoic acid. The key cyclisation-dehydrogenation step between 2-amino-pyrrolidinobenzamide **5** and different benzaldehydes employs $NaHSO_3$ as the dehydrogenating agent in hot DMA. This last reaction shows a strong dependence on the position of the substituent at the aromatic ring of the benzaldehyde used. Thus, the 2-substituted benzaldehydes, in contrast to 3- and 4-substituted compounds give a poor yield of desired products or a mixture.

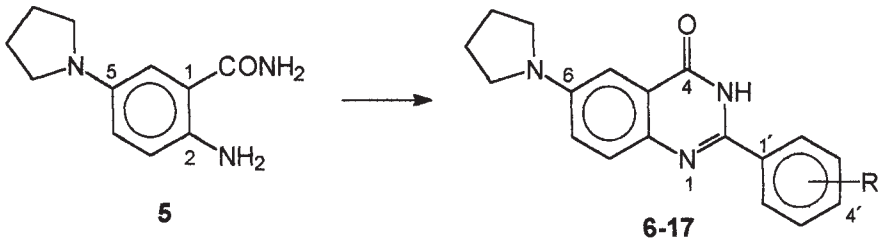
The 2-alkyl and aryl 4(3*H*)-quinazolinones have been prepared by different methods, which include direct synthesis and cyclodehydration of the isolated intermediate 2-(N-acylamino)-benzamide, from 2-aminobenzamides and different carboxylic acid derivatives [10–13] and, more recently, direct oxidation and condensation of 2-aminobenzonitriles.[14] Perhaps, the most common and widely employed method for the synthesis of these quinazolinones is the acylation–cyclisation of anthranilic acid derivatives.[13,15,16] Imai *et al*. briefly reported that 4(3*H*)-quinazolinones could be obtained by the direct cyclocondensation-dehydrogenation of unsubstituted 2-aminobenzamides and some aldehydes in the presence of $NaHSO_3$/DMA, arising from their designed methodology for the synthesis of 2*H*-1,2,4-benzothiadiazine 1,1-dioxides.[17] We have adapted their procedure for preparing our target quinazolinones (Scheme 1).



Scheme 1

* To receive any correspondence.

Table 1



Entry	Compd	R	Yield (%)	Mp (°C)	Rec. solvent	Formula
1	**6**	2-OMe	a	a	a	$C_{19}H_{19}N_3O_2$
2	**7**	3-OMe	85	257-258	DMF	$C_{19}H_{19}N_3O_2$
3	**8**	4-OMe	73	247 *d*	DMF	$C_{19}H_{19}N_3O_2$
4	**9**	3-F	78	255 *d*	DMF	$C_{18}H_{16}FN_3O$
5	**10**	2,3-$(OMe)_2$	b	b	b	$C_{20}H_{21}N_3O_3$
6	**11**	3,4-$(OMe)_2$	47	264 *d*	DMF	$C_{20}H_{21}N_3O_3$
7	**12**	3-Br	82	256-257	DMF	$C_{18}H_{16}BrN_3O$
8	**13**	2-Cl	c	c	c	$C_{18}H_{16}ClN_3O$
9	**14**	4-Cl	83	285-286	DMF	$C_{18}H_{16}ClN_3O$
10	**15**	4-Me	89	276-277	DMF	$C_{19}H_{19}N_3O$
11	**16**	3,4,5-$(OMe)_3$	86	278-279	DMF	$C_{21}H_{23}N_3O_4$
12	**17**	3-Cl	80	271-272	DMF	$C_{18}H_{16}ClN_3O$

a, Only a complex decomposition mixture could be isolated. b, Only the 1,2-dihydro derivative **18** was formed. c, 1,2-dihydro-4(3*H*)-quinazolinone / 4(3*H*)-quinazolinone mixture (8:2), determined by the ^{1}H NMR spectra. *d*, decomposition.

We started from the commercially available 2-nitro-5-chlorobenzoic acid **1**. Thus, the treatment of **1** with 5 equiv of $SOCl_2$ in refluxing benzene for 12 h afforded the acid chloride **2**, which was used in crude form for the next step. Compound **2** was converted by aqueous ammonia into the 2-nitrobenzamide **3**, which was further substituted with pyrrolidine at the position 5 and gave the 2-nitro-5-pyrrolidinobenzamide derivative **4**. The catalytic hydrogenation of **4** using H_2 / 5% Pd/C for 3 h gave the key 2-aminobenzamide **5** with the desired substitution pattern. So, **5** was reacted with different benzaldehydes in the presence of 1.5 equiv. of $NaHSO_3$ and hot DMA (150° C) for 3 hours giving, in most cases, the expected 2-aryl-6-pyrrolidino-4(3*H*)-quinazolinones **6–17** (Table 1). When the benzaldehyde used has a substituent at position 2 (entries 1, 5 and 8) the target quinazolinone is formed in poor yield or not at all. A complex decomposition mixture was obtained with 2-methoxybenzaldehyde, and a 1,2-dihydro-4(3*H*)-quinazolinone / 4(3*H*)-quinazolinone mixture (8:2) with 2-chlorobenzaldehyde. Surprisingly, the reaction with 2,3-dimethoxybenzaldehyde gave only the 1,2-dihydro derivative **18** in relatively good yield, instead of the desired dehydrogenated compound. It seemed possible that prolonging the reaction time (*e.g.* 3 to 5 hours) or increasing the temperature (>150°C) may result in the desired dehydrogenation taking place, but only decomposition was observed under these conditions. Evidently, the steric effect of the substituent located at the position 2′ plays an important role in the dehydrogenation of 1,2-dihydro-4(3*H*)-quinazolinones by sodium hydrogen sulfite. This efficient procedure should be taken into consideration because it offers short reaction times and high yields when compared with the classical and widely used cyclisation–dehydration of anthranilic acid derivatives. The 4(3*H*)-quinazolinones here obtained are now to be biologically evaluated as possible new cytotoxic agents. Studies of the reaction by varying the substitution pattern in the aromatic ring on the key 2-aminobenzamide precursor are now being undertaken by our research group.

Techniques used: IR; ^{1}H NMR; ^{13}C NMR

References: 18

Schemes: 1

Tables: 1

Received 23 November 1999; accepted 3 April 2000
Paper 99/07

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