Dipolar Cycloaddition Reactions with Quinazolinones: a New Synthesis of Azoloquinazolinone Derivatives

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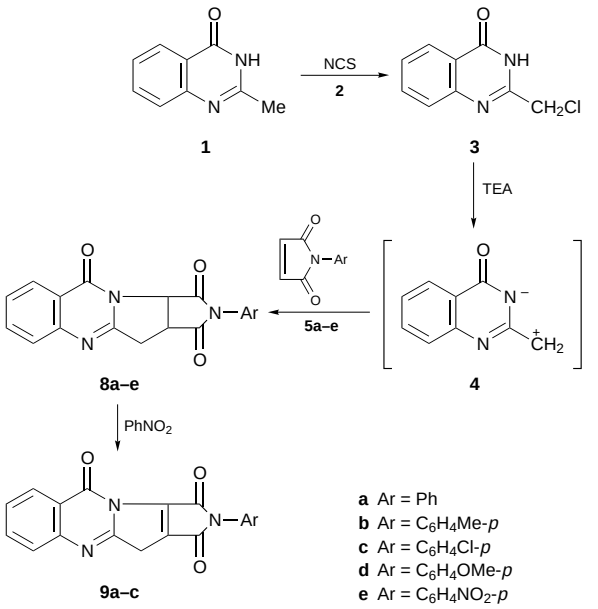
Several new pyrroloquinazolinone derivatives are synthesised *via* a novel route involving the action of dipolarophiles on the diionic species generated *in situ* from the reaction of *N*-chlorosuccinimide with 2-methylquinazolin-4-one and subsequent treatment with triethylamine.

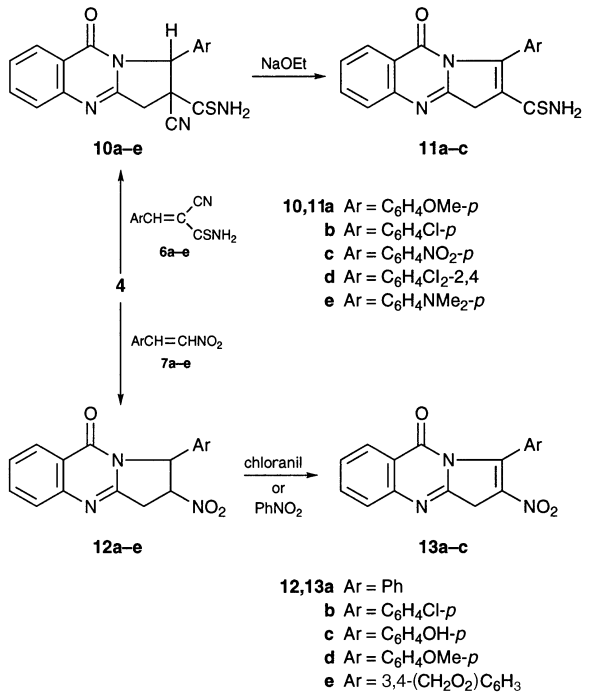
Quinazolin-4-one (**1**) and its annelated azolo derivatives have been found to exhibit antibacterial activity against a variety of organisms, *e.g.* tuberculostatic activity.[1,2] Moreover, the pyrrole moiety is also reported to be an active and essential component in a number of drugs and pharmaceutical preparations controlling infections of bacteria, protozoa and viruses, besides being analgesic and hypnotic.[3-10] The incorporation of the two moieties increases the biological activity of both and thus it was of value to synthesise a number of new heterocyclic derivatives having both these moieties in the same molecules. A novel synthesis was developed which involved the use of *N*-chlorosuccinimide (NCS; **2**) as chlorinating agent.

In continuation our efforts towards the synthesis of biologically active fused heterocycles,[1,2,3] we found that[4,5] 2-methyl quinazoline (**1**) reacted with *N*-chlorosuccinimide (**2**) to yield 2-chloromethylquinazoline (**3**) *in situ* which was separated and the structure confirmed on the basis of its analytical and spectral data [^{1}H NMR 4.56 (s, 2 H, CH_2Cl), 7.53–8.15 (m, 4 H, ArH's) and 12.02 (brs, 1 H, NH)]. Compound **3** was then treated with triethylamine (TEA) to afford the zwitterionic **4** created by the loss of HCl. This zwitterionic species **4** was used as the starting material for the present study and its reactions with some *N*-arylmaleimides **5**, 3-aryl-2-cyanothioacrylamides **6** and ω-nitrostyrenes **7** resulted in the formation of several new azoloquinazolinones required for medicinal studies. A mixture of **1**, *N*-phenylmoleimide (**5a**) and the equivalent amount of TEA in dry chloroform was stirred for 1 h afforded a product of molecular formula $C_{19}H_{13}N_3O_3$ which corresponded to the addition of one molecule of **1** to one molecule of **5a** followed by HCl elimination. The IR spectrum of this reaction product showed the presence of sat. CH_2 and CH (2980 cm^{-1}), CO (1680) and C=N (1630) in addition to the (—CO—NAr—CO—) group as two widely separated bands at 1790 and 1710 cm^{-1}. The ^{1}H NMR spectrum revealed signals for pyrrolidine-CH_2, pyrrolidine H-3 and pyrrolidine H-4 in addition to aromatic protons in their expected positions (*cf.* Experimental, see full text). Based on the above data, this reaction product was formulated as the 3a,11a-dihydro-11*H*-pyrrolo[3′,4′:4,5]pyrrolo[2,1-*b*]quinazoline-1,3,5-trione derivative **8a**. The formation of **8a** in this reaction was assumed to proceed *via* the initial reaction of **1** with **2** to yield *in situ* the non-isolable 2-chloromethylquinazolinone **3**. This reacts with TEA to yield the zwitterionic species **4** which then reacts with **5a** *via* a dipolar cycloaddition reaction to yield isolable **8a**. This reaction constitutes a simple and easy one pot reaction leading to a fused heterocyclic derivative which is otherwise difficult to obtain.

Similarly, compound **4** reacted with each of the *N*-arylmaleimides **5b–e** to give the corresponding pyrrolo-pyrroloquinazolinone derivatives **8b–e** respectively. The structures of **8b–e** were also established on the basis of correct elemental analysis and spectral data which were found to be in good agreement with the assigned structures.



Scheme 1



Scheme 2

On the other hand, dehydrogenation of **8a–c** using either chloranil or nitrobenzene resulted in the formation of the corresponding 11*H*-pyrrolo[3′,4′:4,5]pyrrolo[2,1-*b*]quinazoline-1,3,5-trione derivatives **9a–c** respectively. The structure

*To receive any correspondence.

of **9a–c** was confirmed by elemental analysis and spectral data. The IR spectra of compounds **9a–c** showed the presence of CO (1890) and the (—CO—NAr—CO—) group (1780, 1710) in addition to sat. CH_2 (2980) and C=N (1630 cm^{-1}). The ^1H NMR spectra of compounds **9a**,**c** revealed only signals for pyrroline-CH_2 (d, 4.8) and aromatic protons (m, 7.2–8.0). No pyrrolidine H-3 or H-4 signals were detected in these spectra in accordance with the dehydrogenation reaction.

The behaviour of **4** towards a variety of 3-aryl-2-cyanothioacrylamide derivatives **6a–e** was also investigated.

Thus, it was found that **1** and **4** reacted with 3-*p*-methoxyphenyl-2-cyanothioacrylamide (**6a**) in the presence of TEA to yield a product with molecular formula $C_{20}H_{16}N_4SO_2$ which had an absorption band corresponding to the nitrile function in the IR spectrum. Moreover, pyrrolidine-CH and CH_2 protons were detected by ^1H NMR. Based on the above spectral data, the reaction product was formulated as the thiocarboxamido-3*H*-pyrrolo[2,1-*b*]quinazolin-9-one derivative **10a**. The reaction is assumed to proceed *via* the initial formation of **4** followed by cycloaddition to **6a** to yield the product **10a**.

In a similar manner, each of **6b–e** reacted with **1** and NCS in the presence of TEA to yield the corresponding 2,3-dihydropyrrolo[2,1-*b*]quinazolin-9(1*H*)-one derivatives **10b–e**, respectively. The structures of **10b–e** were also confirmed by elemental analysis and spectral data as for **10a**.

Evidence for the structures of **10a–e** was provided by the action of sodium ethoxide. Thus, each of **10a–e** reacted with boiling sodium ethoxide to give, after acidification, products corresponding to the loss of one molecule of HCN in each case. The IR spectra of these reaction products showed that the bands of the nitrile function were entirely absent. Accordingly, these reaction products were formulated as the thiocarboxamido-3*H*-pyrrolo[2,1-*b*]quinazolin-9-one derivatives **11a–c**, respectively. Moreover, the ^1H NMR revealed pyrroline-CH_2, aromatic and NH_2 protons only.

Furthermore, compound **1** and NCS in chloroform and TEA (*i.e.* **4**) reacted with a variety of ω-nitrostyrenes **7a–e**. Thus **4** reacted with ω-nitrostyrene **7a** to yield the cycloadduct **12a**. IR and ^1H NMR spectra showed the structure to be the 2-nitro-2,3-dihydropyrrolo[2,1-*b*]quinazolin-9(1*H*)-one derivative **12a**. Analogously, each of **7b–e** reacted with **4** to afford the 2-nitro-2,3-dihydropyrrolo[2,1-*b*]quinazolin-9(1*H*)-ones **12b–e**, respectively.

Moreover, compounds **12a–c** could also be dehydrogenated by the action of chloranil to give the corresponding 2-nitro-4*H*-pyrrolo[2,1-*b*]quinazolin-9-one derivatives **13a–c**, respectively. ^1H NMR revealed signals for pyrroline-CH_2 and aromatic protons only.

Techniques used: ^1H NMR, FTIR, elemental analysis

References: 14

Tables 1 and 2: Data for compounds **3**, **8**, **9**, **10**, **11**, **12** and **13**

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