New Synthetic Approaches to Fused Heterocyclo-quinazolines

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Andrea Santagati,*[a] Maria Modica,[a] Luigi Monsù Scolaro[b] and Maria Santagati[a]

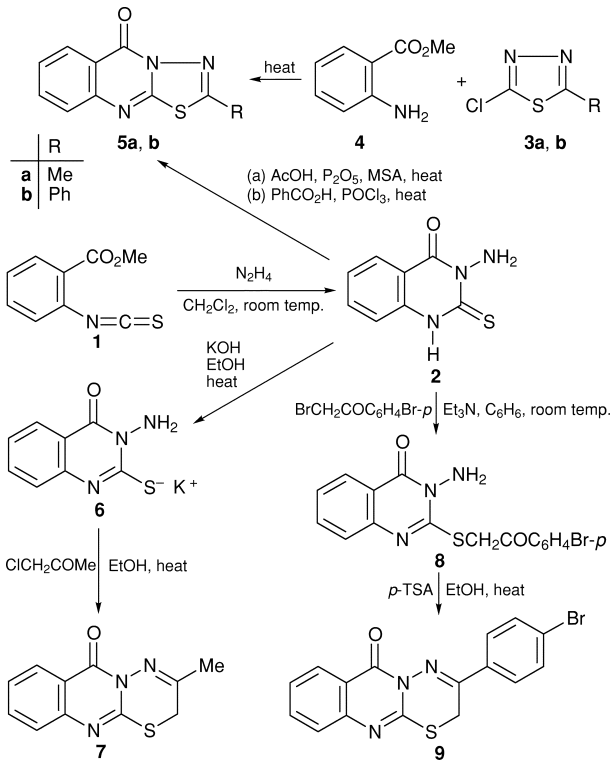
[a]*Dipartimento di Scienze Farmaceutiche, Università di Catania, Città Universitaria, Viale A. Doria, 6, 95125 Catania, Italy*
[b]*Dipartimento di Chimica Inorganica, Analitica e Chimico-Fisica, e ICTPN-CNR, Università di Messina, Villaggio S. Agata, Salita Sperone 31, 98166 Messina, Italy*

Fused heterocyclo-quinazolines have been prepared from the versatile and easily obtained intermediate 3-amino-2,3-dihydro-2-thioxo-4(1*H*)-quinazolinone **2**; their structural elucidation is also reported.

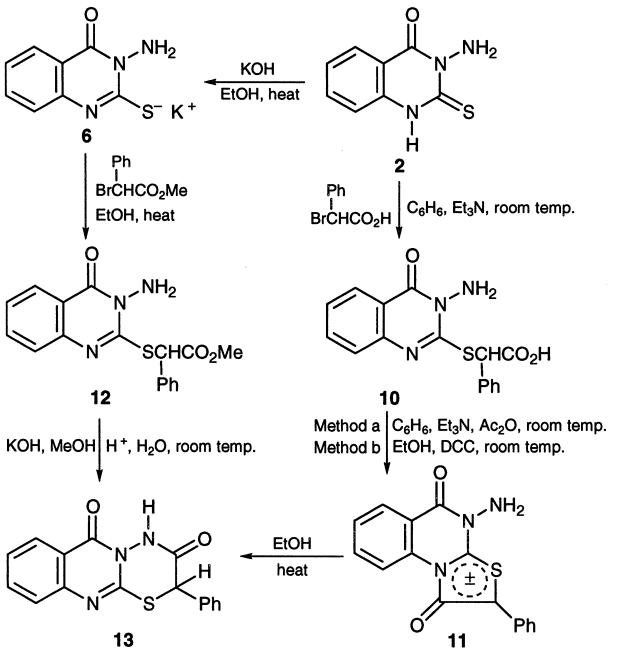
Condensed heterocyclo-quinazolines are a large group of polyheterocycles with diverse, interesting biological activities.[1] Many synthetic methods have been developed to prepare the title compounds but few of them use the versatile and widely synthesized intermediate 3-amino-2,3-dihydro-2-thioxo-4(1*H*)-quinazolinone **2**,[2–5] showing adjacent reactive groups.

In our ongoing search for new heterocycles containing the quinazoline or pyrimidine ring system,[6–13] we now report a new rapid and convenient preparation of the intermediate **2** and, as confirmation of its potentiality in synthetic routes, novel methods for the synthesis (and structural characterization) of some derivatives of condensed heterocyclo-quinazolines (Schemes 1 and 2).

Dropwise addition at room temperature of a solution of isothiocyanate **1**[14,15] in dichloromethane to a stirred solution of hydrazine hydrate in dichloromethane provided in good yields the versatile intermediate **2**. The proposed structure is in agreement with the analytical and spectral data. Reaction of this amino-thioxo derivative **2** with a suitable acid, under appropriate conditions, gave the 2-methyl **5a** and 2-phenyl **5b** -5*H*-[1,3,4]thiadiazolo[2,3-*b*]quinazolin-5-ones, that were



Scheme 1



Scheme 2

proved to be identical with those obtained by Vakula[16] and Russo[6] from the condensation of methyl ester **4** with 3-methyl- or phenyl-2-chloro-1,3,4-thiadiazole **3a** and **3b**, respectively. The synthesis of derivatives **5a** and **5b** allowed us to propose for compound **2** the amino-thioxo structure and to exclude alternative dimeric structures, which may be obtained since hydrazine is a bifunctional reagent.

The 3-methyl[17] **7** and 3-(4-bromophenyl)[3] **9** -2*H*,6*H*-[1,3,4]thiadiazino[2,3-*b*]quinazolin-6-ones were obtained by boiling under reflux in ethanol the potassium salt of the amino-thioxo derivative **2** and chloroacetone, and by cyclizing in refluxing ethanol with a catalytic amount of *p*-toluenesulfonic acid (*p*-TSA) the thio derivative **8**, obtained in benzene from amino-thioxo derivative **2** and 2,4′-dibromoacetophenone in the presence of triethylamine, respectively. The analytical and spectral data of compounds **7**. **8** and **9** are in accordance with the proposed structures; in particular, in the IR and ^{1}H NMR spectra of tricycles **8** and **9** the absence of signals due to NH_2 or NH groups and the presence of signals in the region of δ 4.00 (3.80 for **7** and 4.37 for **9**) attributable to the proton adjacent to a sulfur atom, substantiated the formation of the double bond at the 3,4 position.

The amino-thioxo derivative **2** reacted at room temperature in benzene in the presence of triethylamine with (±)-α-bromophenylacetic acid to give the acid derivative **10**. Compound **10**, when treated in benzene with a mixture of acetic anhydride and triethylamine (v/v 1:1), or by stirring

*To receive any correspondence.

at room temperature in ethanol with an equimolar amount of *N*,*N*-dicyclohexylcarbodiimide (DCC), cyclized to give compound **11**, a molecule, having a mesoionic system, which contains a 'masked' dipole.[18]

Prolonged heating of the mesoionic compound **11** in ethanol gave the dione derivative **13**, which was identical with the product obtained from alkaline hydrolysis of the methyl ester **12** in methanol.

Analytical and spectral data are in accordance with the proposed structure for compounds **10**, **11**, **12** and **13**. The mesoionic compound **11**, in the IR and ^{1}H NMR spectra, exhibits signals attributable to the presence of an NH_2 group; the aromatic protons fall in the range δ 6.93–8.30 with the exception of the C9-proton which exhibits a remarkable downfield shift as a doublet at δ 9.94–9.98, attributable to the anisotropy of the carbonyl group in position 2; in the mass spectra the molecular ion at *m*/*z* 309 (82%) is confirmed, while the presence of a signal at *m*/*z* 121 (30%), attributable to the fragment [$PhCS^+$], corroborates the reaction of the thioxo group with (±)-α-bromophenylacetic acid and the formation of thiazolo-[3,2-*a*]quinazoline system.[19]

The ^{13}C NMR characterization of the mesoionic compound **11** was not possible because this compound has a very low solubility in common NMR solvents and, during the long time (12 h) of acquisition, it is involved in equilibrium with tricycle **13** and the acid derivative **10**.

The linear structure of the dione derivative **13**, as opposed to the angular one, is confirmed in the ^{1}H NMR and IR spectra by the presence of the amidic hydrogen as a broad singlet signal at δ 12.21 and at 3190 cm^{-1}, by the C2-proton as a singlet at δ 5.59, and by the aromatic protons as a multiplet at δ 7.29–8.16.

Techniques used: IR, ^{1}H and ^{13}C NMR, elemental analysis, TLC and mass spectrometry

References: 19

Schemes: 2

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