A new approach to the synthesis of fused heterocyclic compounds. [2+4]-Cycloaddition of 2-heteroarylcyclohexane-1,3-diones to Schiff bases

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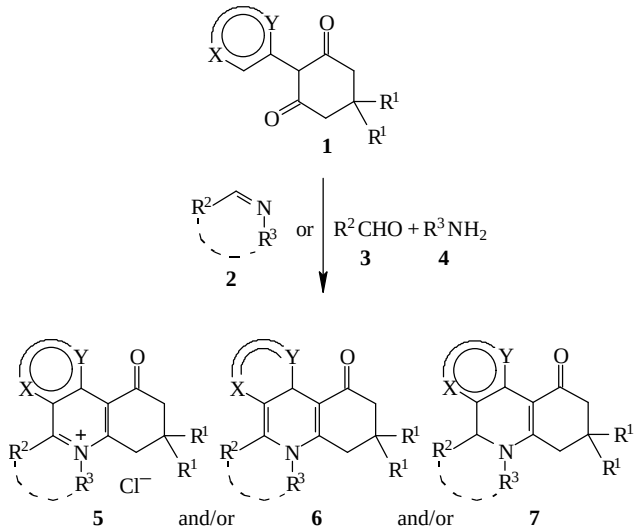
A new approach to the synthesis of fused nitrogen-containing heterocyclic compounds has been developed, involving cyclocondensation of Schiff bases or their synthetic precursors with 2-heteroarylcyclohexane-1,3-diones.

The general strategy for the synthesis of monocyclic and fused nitrogen-containing heterocyclic compounds (azines) involves condensation of carbonyl, β-dicarbonyl and β,β'-tricarbonyl compounds and their derivatives, taken in various combinations, with amines, azomethines and other mono- and bi-functional nitrogen-containing bases.[1a–d] Despite the fact that this synthetic approach has been developed for a fairly long period (its development was started by A. Hantzsch, O. Doebner, L. Knorr, A. Combers and other researchers),[2] its synthetic potential has not yet been exhausted. This is confirmed by the results of studies carried out in recent years.[3a–d] Among the diversity of methods based on this strategy those methods which make it possible to design pharmacophores of natural and synthetic bioregulators, for example, benzo[*a*]-,[3a,d] dibenzo[*a*,*f*]-[4a–c] and other quinolizine (azine) derivatives,[3b,c] are the most valuable. It is clear that only one structural unit can be obtained within the framework of each particular method. Therefore, new approaches to the synthesis of units containing another set of functional groups arranged in a different way (which can serve as a basis for subsequent transformations or for the investigation of the relationship between the structure and biological properties) present essential theoretical and practical interest.

In a study of the interaction of Schiff bases with 1,3-dicarbonyl compounds,[3a–d] we have found a new reaction which can formally be described as [2+4]-cycloaddition of 2-heteroaryl-substituted cyclohexane-1,3-diones **1** to Schiff bases **2**. Judging from the final result, this reaction can be defined as cyclocondensation of the Schiff bases **2** with 2-heteroaryl-(*viz.*, thiazolyl or pyrazolyl)-cyclohexane-1,3-diones **1** or as annelation of Schiff bases with the β-diketone derivatives mentioned above. It was shown that both cyclic (3,4-dihydroisoquinolines[5a,b,d]) and acyclic (benzalanilines[5c]) Schiff bases **2** can be introduced in this.† On the other hand, not only benzalanilines but also their synthetic precursors (aldehydes **3** and amines **4**) can enter into this reaction; this



R^1 = H, Me; R^2 = Ph, 4-$MeOC_6H_4$; R^3 = Ph, 4-MeC_6H_4;
R^2R^3 = –$C_6H_4CH_2CH_2$-*o*-, 6,7-$(MeO)_2C_6H_2CH_2CH_2$-*o*-;
R^4, R^5 = H, Ph; X–Y = –CH=N–NR^4–, –S–C(NHR^5)=N–

Scheme 1

makes it possible to accomplish a one-pot version of this process[5e] thus avoiding the imine synthesis stage. When 3,4-dihydroisoquinolines **2** are used as the substrates, the reaction yields dibenzo[*a*,*f*]heteroaryl[*h*]quinolizinium **5** or -quinolizidin **6**,**7** derivatives.[5a,b,d] The reactions involving benzalanilines **2** or their precursors **3** and **4** lead to heteroaryl[*c*]quinolinium derivatives **5**.[5c,e] In general, the reaction in question can be represented by Scheme 1.

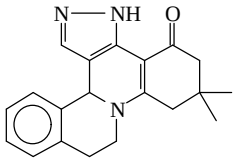
The Scheme indicates that the Schiff base **2** furnishes the forming pyridinium ring with a two-membered carbon–nitrogen fragment, while heteroaryldiketone **1** provides the adjacent fragment containing four carbon atoms. However, 1-alkyl-3,4-dihydroisoquinolines or, in the general case, disubstituted Schiff bases (azomethines) cannot be involved in this reaction; this points to an important role of the steric factor and restricts somewhat the field of applicability of the procedure.

Dibenzo[*a*,*f*]pyrazolo[*h*]quinolizidines **8** and **9**‡ were obtained in this way from 3,4-dihydroisoquinoline and 2-(pyrazol-5-yl)dimedone. The reaction of 3,4-dihydroisoquinoline with 2-(1-phenylpyrazol-5-yl)dimedone resulted in the formation of the iminium derivative **10**,‡ whereas the interaction of *N*-(4-methoxybenzylidene)toluidine with 2-(2-phenylaminothiazol-4-yl) hydrochloride afforded thiazolo[*c*]quinolinium derivative **11**,‡ which has also been prepared by a one-pot modification of the reaction.

The 3,4-dihydroisoquinolines **2** used in this method were obtained by the Bieshler–Napieralski reaction,[8] while

† *General procedure for cyclocondensation.* An equimolar mixture of a Schiff base or its hydrochloride with 2-heteroaryl-1,3-diketone or its hydrochloride was boiled under reflux under an argon atmosphere in ethanol, an ethanolic solution of HCl or acetic acid. The course of the reaction was monitored by TLC on Silufol UV-254 plates using a 4 : 1 chloroform–ethanol mixture as the eluent. The plates were visualised by exposure to UV irradiation or to iodine vapour followed by heating to 250–350 °C. The reaction was usually completed over a period of 3–9 h; however, in some cases,[5b,d] it lasted for 16–48 h. If the product did not separate in the solid state during the process, the reaction mixture was concentrated and allowed to stand at 0–5 °C or the product was precipitated with ether. If these operations did not lead to isolation of the reaction product or if more than one product was present in the reaction mixture, the mixture was concentrated to dryness, and the residue was dissolved in water and extracted with chloroform. As a result, the azine derivative **5**, **10** or **11** remained in the aqueous phase, while the non-azinium product passed into chloroform. To isolate the azinium product, the aqueous phase was saturated with sodium chloride and extracted with chloroform. The collected extracts were dried, filtered and concentrated, and the residues were crystallised from appropriate solvents (usually from chloroform–hexane or ethanol–ether mixtures). All details of the above procedure are also applicable to the one-pot reaction.

‡ Compound **8** (47%), mp 180–182 °C, yellow crystals. Compound **9** (40%), mp205–207 °C, yellow crystals. Compound **10** (83%), mp286–287 °C, white crystals. Compound **11** (71%), mp240–241 °C, a solvate crystal with 1 mol H_2O, yellow crystals.



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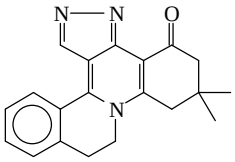

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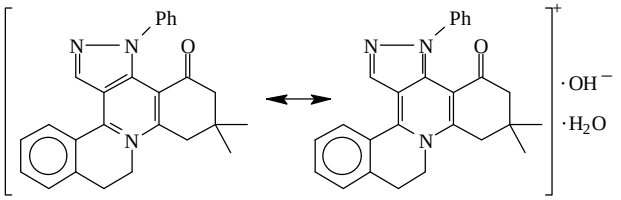

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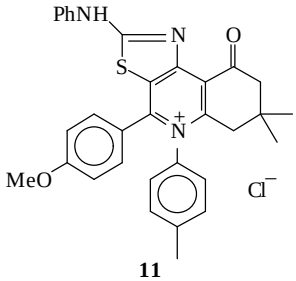

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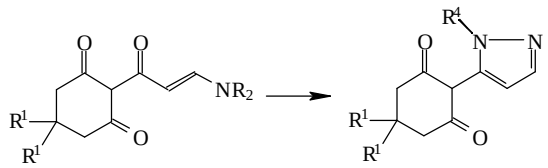
benzylideneanilines **2** were prepared using the general synthetic procedure.[9] 2-(Thiazol-4-yl)cyclohexane-1,3-diones were easily synthesised by a previously described procedure,[6a–c] whereas 2-(pyrazol-5-yl)cyclohexane-1,3-diones **1** were synthesised from enaminotriketones **12**[7a,b] and the corresponding hydrazines,[§] according to Scheme 2:

The approach described above is a further development of the block scheme for the design of carbo- and hetero-cyclic bioregulators.[10a,b] Even now, this scheme demonstrates[5a–e] its significant synthetic potential and, in fact, it is a new, fairly general, approach to the synthesis of various fused heterocyclic structures incorporating a pyridine ring with a nitrogen atom at the ring junction. The data presented in this paper, as well as the results of earlier studies[3a–d,5a–e] allow one to make a favourable prognosis regarding the extension of this synthetic method to other Schiff bases ranging from acyclic aldimines to complex polycyclic fused structures such as 3,4-dihydro-β-carboline,[11a] 3,4-dihydropyrrolo[1,2-*a*]pyrazine,[11b] 2-(3*H*)-benzoazepine,[11c] *etc.*, and to 2-heteroaryl(aryl)-substituted derivatives of 1,3-dicarbonyl compounds of both the aliphatic and heterocyclic series. On the other hand, the possibility found by us of involving the synthetic precursors of acyclic Schiff bases in this reaction,[5e] which makes it possible to accomplish its one-pot version and connects this process to known synthetic methods (electrophilic aromatic substitution, Pictet–Spengler reaction) opens up new prospects for further theoretical and experimental studies aimed at the development of highly effective biogenetically similar schemes for the construction of practically valuable nitrogen-containing heterocyclic compounds, including natural substances.



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Scheme 2

For all the compounds synthesised, satisfactory elemental analysis data, ^{1}H NMR, ^{13}C NMR, IR and UV spectroscopy and mass spectrometry were obtained.

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§ *Synthesis of 2-pyrazolylcyclohexane-1,3-diones*. A 5% excess of the corresponding hydrazine was added to a solution of 2-(2-dialkylamino-prop-2-enoyl)cyclohexane-1,3-dione in 70% acetic acid. The resulting mixture was heated with continuous shaking until it boiled. In 5–10 min, intense formation of the target pyrazolyl diketone started. Heating was continued for an additional 10–15 min, and then the reaction mixture was diluted with a two- or three-fold excess of water, cooled and kept in the cold for crystallisation to be completed. The product was then filtered off, washed with water in the filter and dried. The pyrazolyldiketones thus obtained were homogeneous according to chromatography and could be used without additional purification.