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Synthesis and structure of new 1,3,5-triazine-pyrazole derivatives

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ABSTRACT

We have studied the reaction of methylenedicarbonyl compounds with 4,6-disubstituted 2-hydrazinyl-1,3,5-triazine in order to obtain novel coupled biheterocyclic aromatic systems with potential bioactivity. Reaction conditions were studied and optimized, and a series of 4,6-disubstituted 2-(1*H*-pyrazolyl)-1,3,5-triazines were obtained with good yield.

It is well known[1] that the substitution of the third chlorine atom in 2,4,6-trichloro-1,3,5-triazine (**I**) is not an easy task. It is possible only in case of using strong nucleophiles. We have studied the convenient method of synthesis of trisubstituted *s*-triazine derivatives using very active and stable quaternary salts (**I**) according to Scheme 1.

It is possible to obtain diverse classes of new derivatives of 1,3,5-triazines using these quaternary salts.[2b–f] We have synthesized new amines, azides, amidooximes, hydrazines, and nitriles among these new derivatives. The compounds with such reactive groups are all suitable for further cyclization reactions. They have been used as initial compounds in the synthesis of 1,3,5-triazine derivatives containing diazoles, triazoles, tetrazoles, pyrroles, and triazolyl-triazine pyrroles.[2b–f]

Compounds of low toxicity with growth-stimulating activity, antidote activity, nontoxic cationic surfactants,[4] and inhibitors of the oil-oxidizing processes[5] have been discovered among these derivatives of 1,3,5-triazines using biological screening methods,[3] some of which are water soluble. It is interesting from a practical point of view that salts (**I**) appeared to be active synthons in the synthesis of effective catalysts for the process of anhydride curing epoxy mixtures.[6] On the other hand, it is well known that pyrazole derivatives also show various biological and pharmaceutical applications. It has been found that these compounds have hypoglycemic activity, and are also known an inhibitors and deactivators of liver alcohol dehydrogenase and oxidoreductases.[7a,b] It has been shown in vivo that some of the pyrazole derivatives have appreciable antihypertensive activity.[7c]

Many *s*-triazine derivatives have a wide spectrum of high biological activity as shown in the literature review above. Thus, synthesis and investigation of new *s*-triazine derivatives coupled with a pyrazolyl ring are an important task. It is known that *s*-triazines containing the pyrazolyl fragment in their structure could be synthesized by cyclotrimerization of aromatic nitriles[8] or from cyanuric chloride by substitution of first or second chlorine atom by the aromatic amines containing pyrazolyl fragment in their structure.[9] Ayyangar and colleagues synthesized *s*-triazinylpyrazoles by the reaction of hydrazinyl-*s*-triazines with 3-iminobutyronitrile and acetoacetic ester.[10] The initial hydrazinyl-*s*-triazines have been synthesized by the direct treatment of monochloro-*s*-triazines with the hydrazine hydrate. In this case the yields of hydrazinyl-*s*-triazines are not very high since initial 2-chloro-4,6-disubstituted-*s*-triazine is insoluble in hydrazine hydrate or in water. The reactions of hydrazinyl-triazines with acetyl acetone or aromatic diketones are unknown. In our ongoing research on the preparation of the new coupled pyrazolyl-1,3,5-triazines, we used quaternary salts **I** as intermediate compounds in the synthesis of the hydrazinyl-triazines **II**, followed by the addition-cyclization reaction with 1,3-diketones according to Scheme 2.

The 2-hydrazinyl-4,6-disubstituted-1,3,5-triazines **II** have been synthesized by the reaction of salts **I** with hydrazine hydrate hydrochloride in a basic solution as described in our previous articles.[6,11] We synthesized the pyrazolyl-triazines **IIIa–g** by the reaction of hydrazinyl-triazines **II** with 1,3-diketones in the presence of

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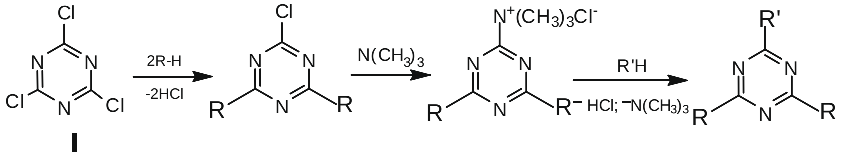


Scheme 1. Synthesis of 2,4,6-trisubstituted 1,3,5-triazines.

a catalytic amount of trimethylamine in a dry toluene solution. Reaction of 1,3-diones with the hydrazine or substituted hydrazines is the most typical method for pyrazole synthesis.[12] The stronger LDA base has been used in the case of the synthesis of polyaromatic pyrazolyl-triazines **IV**. The aromatic 1,3-diketones have been synthesized in situ from the corresponding acetophenone derivatives and benzoylchloride[13] according to Scheme 3.

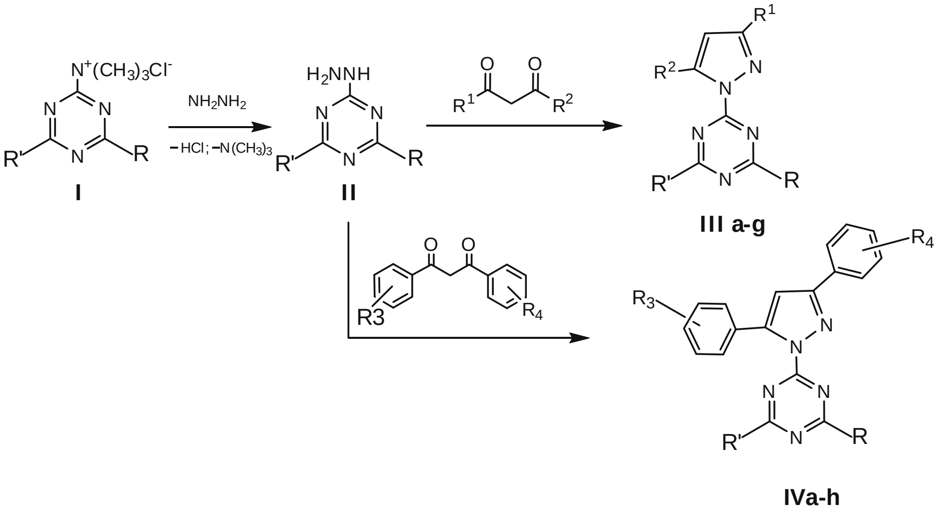
The speed of the reaction of the hydrazinyl-triazines **II** with the 1,3-diketones varies from few hours in case of synthesis of compounds **III** to several days or sometimes even weeks in case of the synthesis of compounds **IV** using aromatic diketones. The progress of the reaction has been monitored using TLC. It is interesting to note that variation of the solvent and catalysts did not affect the rate of reaction or the yield. The final yield for this reaction ranges from 50% to 80%. The new compounds **III–IV** are white or light yellow crystals. They are water insoluble and not very soluble in usual organic solvents, such as ethanol and chloroform. They are soluble in DMF and DMSO and organic solvents with high boiling point. The compounds **III–IV** melt without decomposition between 100 and 206 °C.

The structures of all synthesized compounds have been proven by IR, ^{1}H NMR, ^{13}C NMR, and mass-spectroscopy data (see Table 1).

IR-spectroscopy data of the compounds **III–IV** have variable intensity, sometimes broad absorption bands as well as stretching vibrations typical for the functional groups in their structure. Compounds **III** have medium and strong absorption bands in the area 1528–1525 cm^{-1} typical for the C=C and C=N conjugated. It is interesting, that all of compounds **IV** as well as the compound **IIIf** with the biphenyl substituent have one extra absorption band in this area. Compounds **III** and **IV** (except **III**c) all have two absorption bands in the area 1203–1006 cm^{-1} typical for the C–O–C functional group. IR spectra of compounds **IV** have medium and small absorption bands in the areas 815–806 and 787–773 cm^{-1} typical for the bending vibrations of the 1,3- and 1,4-disubstituted aromatic rings.[14]

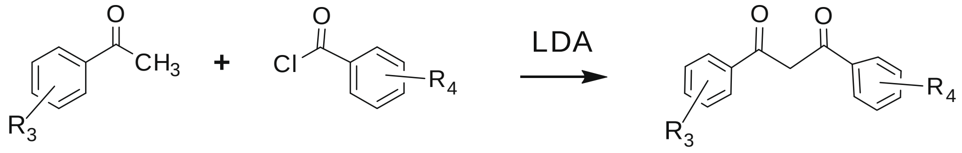
^{1}H NMR spectra of all synthesized compounds have signals of all corresponding protons and the integration curves prove the number of protons. The single proton of the pyrazole ring has a signal in the area of 5.66–6.78 ppm. Two methyl groups of the pyrazole ring have two singlet signals in the area 2.03–2.8 ppm. Compound **IIId** is an exception since it has only one methyl group attached to the pyrazole ring. The 10 phenyl protons of the NPh$_2$ group in compound **IIIf** appear as a broad multiplet signal in the area of 7.26–7.42 ppm and cannot be differentiated. We can say the same about phenyl and phenylene protons of compounds **IV**. Only for the NMR spectra of **IVc** and **IVe** the separation of the signals typical for these protons into four multiplets with the maximums at 6.90–7.96 ppm can be observed. This is most likely due to the structural distinction of these compounds. The protons of the morpholyl and piperidyl rings of derivatives **III** and **IV** appeared as multiplet signals.

The mass spectroscopic molecular ions observed in the spectra of compounds **IIIa–g** and **IVa**, **d**, **g** also confirm their structure. Compounds **IIIc** and **IIId** have the maximum intensity of the molecular ions. Hence, the character and the way of the fragmentation of the molecular ions under the electronic impact are the same as it has been observed for the earlier synthesized heterocyclic derivatives of the 1,3,5-triazine.[2c–f]



IIIa-c R = piperidino, R^1 = R^2 = CH$_3$, R' = OCH$_3$ **IIIa**, NEt$_2$ **IIIb**, piperidino **IIIc**; **IIId-g** R = morpholino; R' = OCH$_3$ **IIId,e**, NPh$_2$ **IIIf**, morpholino **IIIg**; R^1 = R^2 = CH$_3$ **IIIe-g**; R^1= CH$_3$, R^2 = CF$_3$ **IIId**; **IVa-e** R = OCH$_3$, R' = piperidino **IVa,b**, R'= morpholino **IVd**; R=R'= piperidino **IVf;** R=R'= morpholino **IVg**; R=R'= OCH$_3$ **IVc**; R^3 = *m*-OCH$_3$ **IVa,b,d,g**; *p*-OCH$_3$ **IVc,e,f**; R^4 = H **IVa,d,g**; *p*-Br **IVb,c,e,f**.

Scheme 2. Synthesis of the 2,4-disubstituted-6-pyrazolyl (or substituted pyrazolyl)-1,3,5-triazines.



Scheme 3. Synthesis of arylsubstituted 1,3-diones.

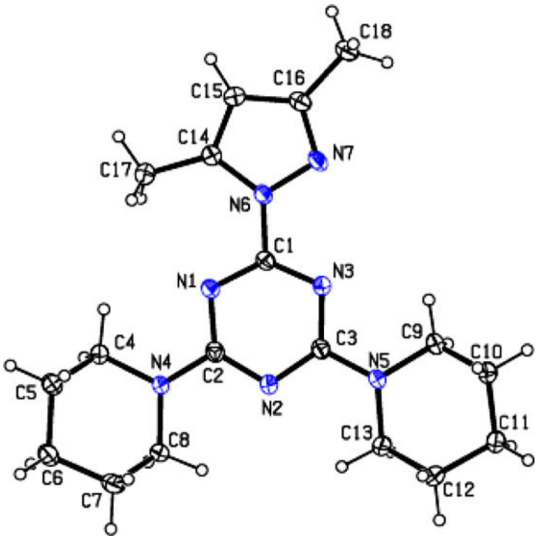


Figure 1. Crystal structure of compound **IIIc**.

To study the fine structure of the resulting pyrazolyl-triazines, we carried out X-ray diffraction for compound **IIIc** whose crystals were grown from an *iso*-propanol/water mixture. The projection of the three-dimensional structure of the derivative **IIIc** is shown in Figure 1. Selected interatomic distances and bond angels are given in Tables 2 and 3, respectively. The complete tables of aromatic coordinates, thermal parameters, bond lengths, and bond angles were deposited with the Cambridge Structural Database.

The pyrazolyl-triazine ring system in molecule **IIIc** is mainly planar. As can be seen from Table 2, the bond lengths in the triazine ring are slightly distorted and vary from 1.356 (N(1)–C(2)) to 1.318 (N(3)–C(3)), which is somewhat different from the bond lengths in non-substituted *s*-triazines.[15–19] (1.337 Å). The 1,3,5-triazine ring is unsymmetrical with the bond angles (see Table 3) at the nitrogen atoms in the ring are distorted (112.72° (N(1))–114.67° (N(2)) and differ substantially from the bond angels at the carbon atoms (125.22° (C(3))–129.03° (C(1)). The bond lengths and angles of the pyrazole ring are slightly different from the non-substituted pyrazole ring. The C(14)–N(6) (1.378 Å) and N(6)–N(7) (1.380 Å) are longer than the same bonds in non-substituted pyrazole ring (1.356 and 1.365 Å, respectively).[17] This is probably due to the conjugation with the 1,3,5-triazine ring. The bond angels vary from 105.2° (N(7)) to the 110.6° (C(16)) and this is close to the angle values of the unsubstituted pyrazole. Both piperidine rings have a chair conformation, and the bond lengths and angles agree well with the average values observed in cyclic nonaromatic amines.

In summary, a series of new 1,3,5-triazine derivatives containing the pyrazole fragment and triazine ring together with high bioactivity potential have been prepared.

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Supplementary data

The physico-chemical characteristics and some X-ray data for the new compounds (Supplementary data Tables 1, 1a, 2, and 3) as well as experimental part could be found in the supplementary data. CCDC 715781 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.03.054.

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