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Synthesis of novel 2,5-dihydro- and 2,3,4,5-tetrahydro-1,2,4-triazin-5-ones from 2-arylhydrazonoacetamides and orthoesters

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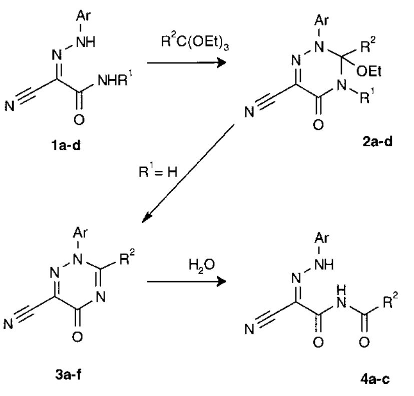
Reactions of 2-arylhydrazonoacetamides **1** with orthoesters were shown to give, depending on the structure of the hydrazone and the reaction conditions, either 2,3,4,5-tetrahydro-1,2,4-triazin-5-ones **2** or 2,5-dihydro-1,2,4-triazin-5-ones **3**, which are very susceptible to hydrolysis to form 2-arylhydrazono-N-acylacetamides **4**.

Only a few methods to prepare 1,2,4-triazin-5-ones have been published, including the reactions of amidrazones with α-ketoacetic acid derivatives[1] and oxidation of preformed 1,2,4-triazines by various oxidizing reagents.[2] Therefore, the substitution pattern of the known 2,5-dihydro and 2,3,4,5-tetrahydro-1,2,4-triazin-5-ones which are available is limited to N-alkyl and N-unsubstituted derivatives. At the same time, 1,2,4-triazines, which are the aza analogues of the pyrimidine bases of nucleic acids are of importance for the study of their biological activity. Now we report a novel method for the synthesis of 2,3,4,5-tetrahydro-1,2,4-triazin-5-ones **2** and 2,5-dihydro-1,2,4-triazin-5-ones **3** based on reactions of 2-arylhydrazonoacetamides **1** with orthoesters.

Results and discussion

Reactions of 2-arylhydrazonoacetamides with orthoesters have been scarcely described.[3] We have now studied this reaction for a number of 2-arylhydrazono-2-cyanoacetamides **1d–g** with triethyl orthoformate, orthoacetate and orthopropionate in various solvents and at various temperatures. The 2,5-dihydro-2-aryl-3-cyano-1,2,4-triazin-5-ones **3a–f** were obtained as single products in high yields when this reaction was carried out in boiling *m*-xylene for 10 h.

2,5-Dihydro-2-aryl-3-cyano-1,2,4-triazin-4-ones **3a–f** are crystalline compounds with high melting points. It is known that the 1,2,4-triazine ring is stable towards acids and bases. The ring is able to add water in acidic medium to form an adduct where water has reacted with the C^3=N bond. The triazine can be recovered from this adducts in the presence of a base.[2]



R^2= H

1,2	R^1	Ar
a	Me	C_6H_4OMe-*p*
b	Me	Ph
c	Me	C_6H_4Cl-*p*
d	H	$C_6H_4CO_2Et$

1	R^1	Ar
e	H	C_6H_4OMe-*p*
f	H	Ph
g	H	C_6H_4Cl-*p*

3, 4	R^2	Ar
a	H	C_6H_4OMe-*p*
b	H	Ph
c	H	C_6H_4Cl-*p*
d	H	$C_6H_4CO_2Et$-*p*
e	Me	Ph
f	Et	Ph

Scheme 1

2,5-Dihydro-2-aryl-3-cyano-1,2,4-triazin-5-ones **3** are also capable of adding water to form, in contrast to known 1,2,4-triazines, dicarbonyl compounds **4a–c** which are products resulting from the cleavage of the N^2–C^3 bond**.**

The structures of the 2-arylhydrazono-N-acylacetamides **4a–c** were supported by their IR spectra which show strong cyano and carbonyl bonds stretching at 2200 and 1720–1730 cm^{-1}. ^{1}H and ^{13}C NMR, and mass-spectra also confirmed their structures.

We have found that three types of products are formed in the reaction of hydrazone **1d** with triethyl orthoformate while refluxing either in DMF solution for 3 h or in toluene solution for 30 h.

These results prompted us to investigate whether N_4-alkyl derivatives of 2,3,4,5-tetrahydro-1,2,4-triazin-5-ones would be stable compounds and if they could be prepared in the reaction of alkylamides of 2-arylhydrazonoacetic acids **1a–c** with orthoesters. Indeed, treatment of hydrazones **1a–c** with triethyl orthoformate under reflux leads to the formation of triazines **2a–c**, bearing a methyl group at position 4 of the ring.

The novel tetrahydrotriazines **2** are crystalline compounds. They are stable towards treatment with either bases or acids at room temperature. However, boiling an ethanolic solution of compound **2** in the presence of an equimolar amount of sulfuric acid leads to their degradation to form starting hydrazones **1**.

In conclusion, we have proved that the triazine derivatives **2** and **3** are intermediates in the acylation reaction of 2-arylhydrazonoacetamides **1** with orthoesters, yielding acylamides **4**. In this work it was found that by changing the reaction conditions one could obtain either tetrahydrotriazines **2** or dihydrotriazines **3**.

Table 1	Analytical data for compounds **2**–**4**
Table 2	IR and ^{1}H NMR spectra of compounds **2–4**
Table 3	^{13}C NMR data for compounds **2a–c**, **3b**, **3e** and **4a**
Table 4	Mass spectral data for triazines **2** and **3,** *m/z* (%)

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