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Asymmetric induction in the reactions of 3-aryl-1,2,4-triazin-5(4*H*)-ones with C-nucleophiles

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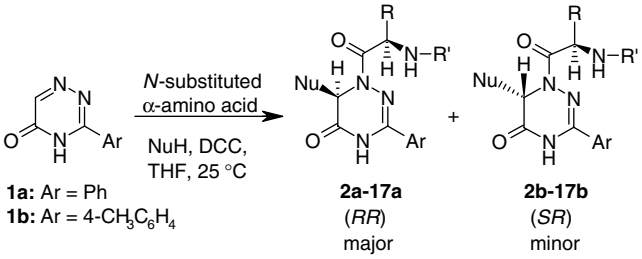
Abstract—3-Aryl-1,2,4-triazin-5(4*H*)-ones, in the presence of N-protected amino acids, react with C-nucleophiles to form 1-acyl-6-Nu-3-aryl-1,6-dihydro-1,2,4-triazin-5(4*H*)-ones in high diastereomeric excess. This is the first case of the use of amino acids as chiral auxiliaries in nucleophilic additions to triazinones.

It is known that the nucleophilic addition of C-nucleophiles to a prochiral C=N double bond in azines in the presence of optically active acylation reagents results in the formation of compounds containing two stereocenters, and sometimes proceeds with a high diastereoselectivity.[1]

We found that 3-aryl-1,2,4-triazin-5(4*H*)-ones (**1a**,**b**) could be acylated with N-substituted L-,D- and D,L-amino acids in the presence of DCC and then further react with indoles to form 1-(2-aminoacyl)-6-Nu-3-aryl-1,6-dihydro-1,2,4-triazin-5(4*H*)-ones (**2a**–**17a**) in high diastereomeric excess (Scheme 1, Table 1).[2]



Scheme 1.

^{1}H NMR analysis of the crude mixtures of **2a**–**17a** indicated the predominant formation of one diastereomer in each case and only one pair of diastereomers in purified products.

In order to establish the stereochemistry, X-ray analysis of compound **13a** was performed confirming that **13a** was a pair of *SS*, *RR*-enantiomers (Fig. 1).

We can propose two reaction pathways for product formation. Pathway **A** involves initial in situ generation of chiral 1-acylazinium salt **1***,[4] which reacts further with nucleophiles to form adducts **2a**–**17a**. Pathway **B** proceeds with the initial formation of adducts **18a**,**b** and subsequent reaction with the activated amino acid (Scheme 2).

In a previous work it was shown that triazines **1** react with C-nucleophiles in boiling butanol or in acetic acid with the formation of 6-Nu-3-aryl-1,6-dihydro-1,2,4-triazin-5(4*H*)-ones **18**.[5] We thus considered pathway **B**. It turned out that the reaction of compounds **18** with activated amino acids under identical conditions to those described for triazinone **1** resulted in the formation of two pairs of diastereomers (Scheme 3, Table 2). ^{1}H NMR analysis of the products showed two sets of signals. Thus, we come to the conclusion that the reaction shown in Scheme 1 proceeds by means of the formation of intermediate acylazinium salt **1***, leading to the diastereoselective formation of products **2a**–**17a**, in contrast to pathway **B**, which leads to the formation of two pairs of diastereomers.

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Table 1. The reaction of triazinones **1a**,**b** with amino acids and C-nucleophiles

NuH	Ar	N-substituted α-amino acid	Ratio **a**:**b**,[a] %	Product	Yield, %	Configuration
Indole	Ph	*N*-Boc-glycine	—	**2a**	48	—
Indole	Ph	*N*-Bz-D,L-leucine	>95:5	**3a**	34	*SS*, *RR*
Indole	Ph	*N*-Formyl-D-alanine	>95:5	**4a**	28	*RR*
Indole	Ph	*N*-Acetyl-L-tryptophan	>95:5	**5a**	21	*SS*
Indole	Ph	*N*-Acetyl-D,L-phenylalanine	>95:5	**6a**	22	*SS*, *RR*
Indole	4-$CH_3C_6H_4$	*N*-Acetyl-L-valine	95:5	**7a**	24	*SS*
Indole	4-$CH_3C_6H_4$	*N*-Acetyl-D-alanine	95:5	**8a**	15	*RR*
Indole	4-$CH_3C_6H_4$	*N*-Acetyl-D,L-phenylalanine	95:5	**9a**	22	*SS*, *RR*
Indole	4-$CH_3C_6H_4$	*N*-Acetyl-L-tryptophan	>95:5	**10a**	18	*SS*
Indole	4-$CH_3C_6H_4$	*N*-Acetyl-D-tryptophan	>95:5	**11a**	16	*RR*
Indole	4-$CH_3C_6H_4$	*N*-Acetyl-D,L-tryptophan	95:5	**12a**	25	*SS*, *RR*
2-Me-indole	Ph	*N*-Bz-D,L-leucine	>95:5	**13a**	36	*SS*, *RR*
2-Me-indole	Ph	*N*-Acetyl-L-tryptophan	>95:5	**14a**	25	*SS*
2-Me-indole	4-$CH_3C_6H_4$	*N*-Acetyl-L-valine	>95:5	**15a**	22	*SS*
1-Me-indole	4-$CH_3C_6H_4$	*N*-Bz-D,L-leucine	>95:5	**16a**	30	*SS*, *RR*
1-Me-pyrrole	4-$CH_3C_6H_4$	*N*-Bz-D,L-leucine	>95:5	**17a**	14	*SS*, *RR*

[a] Isomer ratio in crude mixture (determined by ^{1}H NMR).

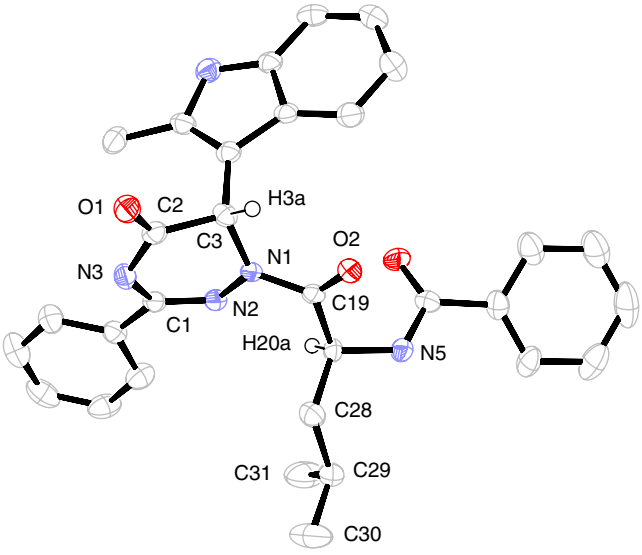
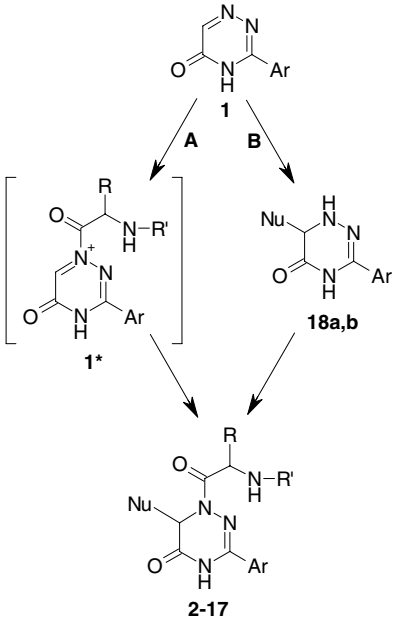
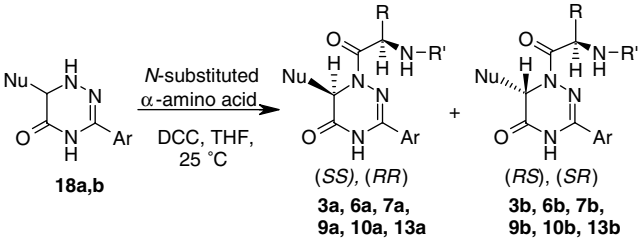


Figure 1. ORTEP diagram of the X-ray crystal structure of **13a**.[3]



Scheme 2.



Scheme 3.

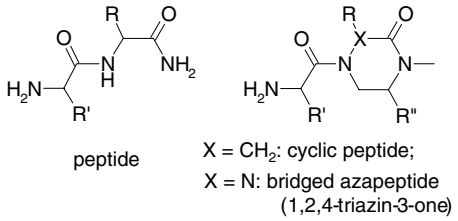
Compounds **2a**–**17a** can be considered as peptidomimetics, that is, compounds having structures similar to peptides.[6] Some cyclic peptidomimetics based on 1,2,4-triazin-3(2*H*)-ones (bridged azapeptides) are known (Scheme 4).[7]

In conclusion, two approaches to the synthesis of a series of novel peptide mimetics **2a**–**17a** were examined,

Table 2. The reaction of compounds **18a**,**b** with amino acids and C-nucleophiles

Nu	Ar	N-substituted α-amino acid	Ratio **a**:**b**,[a] %	Product	Yield **a** + **b**, %	Configuration **a**; **b**
Indole	Ph	*N*-Bz-D,L-leucine	80:20	**3a** + **3b**	52	*SS*,*RR*; *RS*,*SR*
Indole	Ph	*N*-Acetyl-D,L-phenylalanine	45:55	**6a** + **6b**	34	*SS*,*RR*; *RS*,*SR*
Indole	4-$CH_3C_6H_4$	*N*-Acetyl-L-valine	50:50	**7a** + **7b**	26	*SS*; *RS*
Indole	4-$CH_3C_6H_4$	*N*-Acetyl-D,L-phenylalanine	45:55	**9a** + **9b**	31	*SS*,*RR*; *RS*,*SR*
Indole	4-$CH_3C_6H_4$	*N*-Acetyl-L-tryptophan	80:20	**10a** + **10b**	46	*SS*; *RS*
2-Me-indole	Ph	*N*-Bz-D,L-leucine	80:20	**13a** + **13b**	38	*SS*,*RR*; *RS*,*SR*

[a] Isomer ratio after crystallization (determined by ^{1}H NMR).



Scheme 4.

one of which was stereocontrolled. We have presented the first example of the use of amino acids as chiral auxiliaries in nucleophilic additions to triazinones.

Acknowledgements

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References and notes

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2. Typical procedure for the synthesis of **2a**–**17a**: To a magnetically stirred suspension of **1** (1 mmol) in 15 ml of dry THF at room temperature, DCC (1.5 mmol) and N-protected amino acid (1.5 mmol) were added. After 15 min, indole (1.05 mmol) was added and the reaction mixture was kept at room temperature for 48 h. The resulting 1,3-dicyclohexylurea precipitate was filtered off and the mother liquid was evaporated. The residue was treated with 15–25 ml of dry ether and the precipitate was filtered off and recrystallized from acetonitrile to afford 14–48% yields of **2a**–**17a**.
3. Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre (deposition number CCDC 270338). These data can be obtained via www.ccdc.cam.ac.uk/data_request/cif.
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