Regioisomeric formation of the linear 1,2,4-triazolo[4′,3′:2,3][1,2,4]triazino[5,6-*b*]indole from 3-hydrazino-1,2,4-triazino[5,6-*b*]indole derivatives

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Oxidative cyclisation of the ethylidene derivatives of 5-allyl-3-hydrazino-1,2,4-triazino[5,6-*b*]indole **(7)** and 8-bromo-3-hydrazino-5*H*-1,2,4-triazino[5,6-*b*]indole **(8)** gave regioselectively the linear isomers, 10-allyl-3-methyl-1,2,4-triazolo[4′,3′:2,3][1,2,4]triazino[5,6-*b*]indole **(15)** and 7-bromo-3-methyl-10*H*-1,2,4-triazolo[4′,3′:2,3][1,2,4]triazino-[5,6-*b*]indole **(16)**, respectively. They were also obtained by the dehydrative cyclisation of **5** and **6** respectively with acetic acid as well as by the condensation of the *N*-allyl- **(22)** or 5-bromo-isatin **(23)** with 3,4-diamino-5-methyl-4*H*-1,2,4-triazole **(24)**. The corresponding allyl derivatives **17** and **18** were also synthesised. Some sugar derivatives of **5** were prepared.

Keywords: fused indoles, fused 1,2,4-triazines, fused 1,2,4-triazoles, oxidative cyclisation, hydrazones

Various heterocyclic compounds incorporating the 1,2,4-triazine ring show interesting biological activities including antihypertensive, antiviral and antibacterial properties,[1-11] as well as activity against *Staphylococcus aureus and Bacillus cereus* and P388 lymphocytic leukemia.[6]

The fusion of a heterocyclic ring to the 1,2,4-triazine ring via a functional group on position-3 may take place at N-2 or N-4 to give a linear[1,2,12-16] or angular[17-20] fused heterocycles, respectively. It has been found that the regioselective annelation of a triazole to a triazine ring[1,2,21-24] can be achieved by the cyclisation of 3-hydrazino-5*H*-1,2,4-triazino[5,6-*b*]indole either via the dehydrative cyclisation of the respective hydrazide or the dehydrogenative cyclisation of the hydrazones to the linear isomer 10*H*-1,2,4-triazolo[4′,3′:2,3][1,2,4]triazino[5,6-*b*]indole.[1,2,21] On the other hand, the regioselectivity was reversed by introducing a methyl group at N-5 or C-8 of the triazinoindole ring,[25,26] when angular isomers were formed. In the present work the cyclisation of 3-hydrazino-5*H*-1,2,4-triazino[5,6-*b*]indoles, with 5-allyl or 8-bromo substituents, with some one-carbon inserting reagents has been investigated in order to find the effect of these substituents on the site of cyclisation. Moreover, the introduction of the allyl group provide derivatives suitable for modification to provide acyclonucleosides.

The starting materials 5-allyl-3-hydrazino-1,2,4-triazino[5,6-*b*]indole **(5)** and the 8-bromo derivative **6** were prepared by the hydrazinolysis of **2** and **4**, respectively. A better yield of **5** could be obtained by the reaction of the S,*N*-diallyl derivative **3** with hydrazine.

Although the cyclisation of the 3-ethylidenehydrazino-5-(or 8-)methyl-1,2,4-triazino[5,6-*b*]indoles gave the angular isomers 1,10 (or 1,7)-dimethyl-1,2,4-triazolo[3′,4′:3,4]-[1,2,4]triazino[5,6-*b*]indoles,[25,26] the introduction of an allyl group instead of the methyl group on N-5 of the indole ring or a bromine atom on the respective 8-position caused a change in the site of cyclization of the respective hydrazones to give the linear isomers. Thus, reaction of **5** or **6** with acetaldehyde gave the 5-allyl-3-ethylidenehydrazino-1,2,4-triazino-[5,6-*b*]indole **(7)** and 8-bromo-3-ethylidenehydrazino-1,2,4-triazino[5,6-*b*]indole **(8)**, respectively. The annelation of the triazole ring to the triazine ring was achieved by oxidation of the hydrazones **7** and **8** with $FeCl_3$/EtOH to give the corresponding triazolo derivatives **15** and **16** rather than **13** and **14**. The selection of the linear isomers was based on a model experiment whereby the synthesis of **15** and **16** was alternatively achieved by the condensation of the *N*-allylisatin **(22)** and 5-bromoisatin **(23)**, respectively, with 3,4-diamino-5-methyl-4*H*-1,2,4-triazole **(24)**. Further confirmation of the structure of **15** was obtained by the allylation of 3-methyl-10*H*-1,2,4-triazolo[4′,3′:2,3][1,2,4]triazino[5,6-*b*]indole to give 10-allyl-3-methyl-1,2,4-triazolo[4′,3′:2,3]triazino-[5,6-*b*]indole **(15)**, which was found to be identical with the products obtained from the above two methods.

Moreover, **15** and **16** were obtained by heating **5** or **6** with acetic acid. On the other hand, when the hydrazine **5** was allowed to react with acetic anhydride, the product was identified as **21** and not the triazolotriazinoindole **15**.

Condensation of **5** with benzaldehyde and *p*-nitrobenzaldehyde gave the corresponding hydrazones **9** and **10**, whose cyclization with $FeCl_3$/EtOH gave **17** and **18**, respectively. The linear structure assigned to these products from the oxidative cyclisation was proved by the identity of the product, triazolotriazinoindole **17**, with that obtained by the allylation of 3-phenyl-1,2,4-triazolo[4′,3′:2,3][1,2,4]triazino[5,6-*b*]indole[21] with allyl bromide. Similarly, **19** and **20** were prepared from **11** and **12**, respectively.

The mode of cyclisation of **7, 9** or **10** may be governed by the steric repulsion between the allyl group at N-5 of the indole ring and the substituent on the hydrazone residue if the cyclisation takes place at N-4. To avoid such steric repulsion, the cyclisation took place at N-2 to give the respective linear isomer. On the other hand, the formation of the linear isomer **16** could be attributed to the electron withdrawing effect of the bromine atom which induces the pair of electrons on N-5 to be less available for contribution in preserving the 10 π-electron system of the indole ring.[1,2] Moreover, the higher nucleophilicity of N-2 than that of N-4 suggested that the cyclization is likely to take place at N-2. A 1,5-proton shift may be operating, enhancing the nucleophilicity of N-2 as shown in Scheme 2.

A series of hydrazones **25** was prepared by the condensation of **5** with the monosaccharides D-galactose, D-mannose, D-arabinose, and L-arabinose. Their IR spectra showed bands at 3356–3374 cm^{-1} (OH) and 3208–3244 cm^{-1} (NH). Acetylation of **25** with acetic anhydride in pyridine gave **26**. The IR spectra of **26** showed the presence of OAc groups (1750–1752 cm^{-1}) and NAc groups (1698-1700 cm^{-1}). The ^{1}H-NMR spectrum of **26a** showed the presence of five OAc groups in addition to a one NAc, confirming its structure. Attempted oxidative cyclisation of the hydrazones **25** with $FeCl_3$ failed to give identifiable products.

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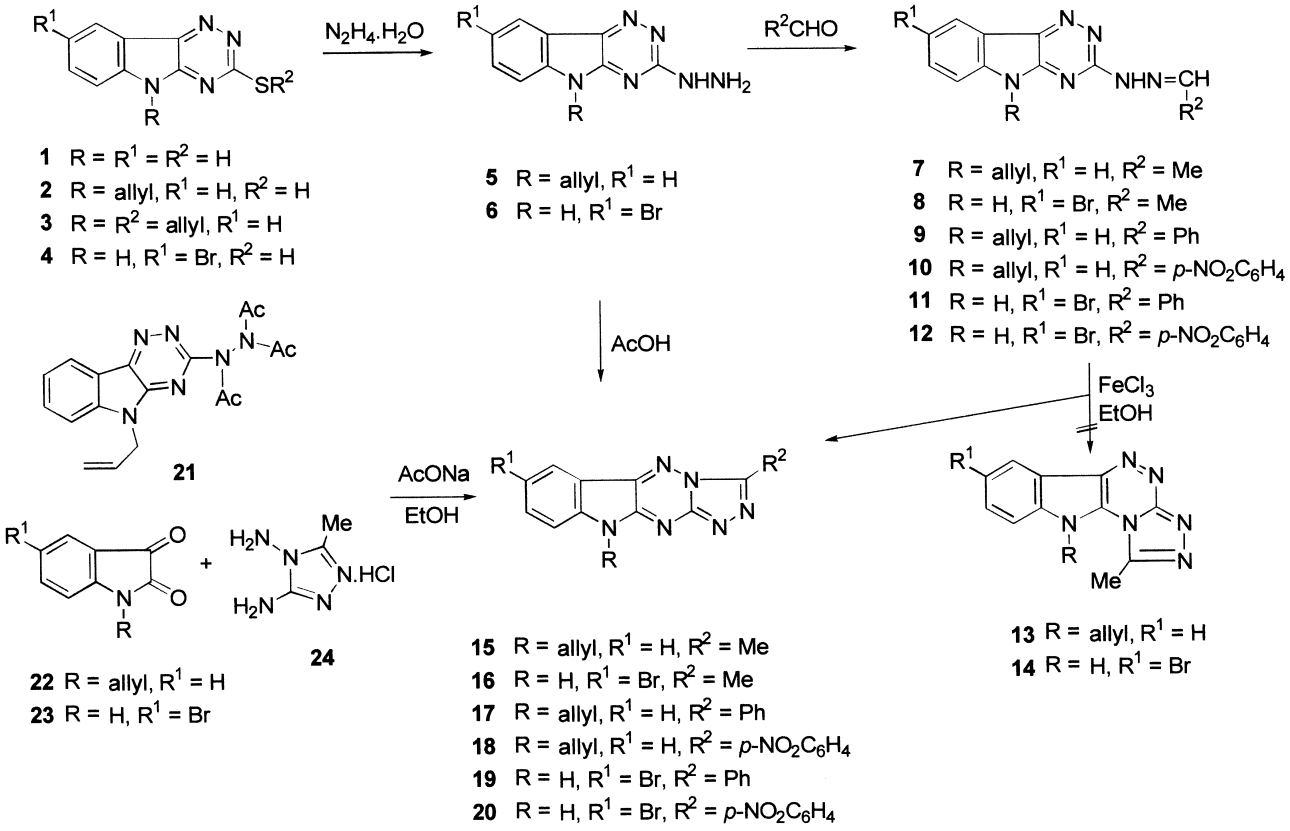


1 R = R^1 = R^2 = H
2 R = allyl, R^1 = H, R^2 = H
3 R = R^2 = allyl, R^1 = H
4 R = H, R^1 = Br, R^2 = H

5 R = allyl, R^1 = H
6 R = H, R^1 = Br

7 R = allyl, R^1 = H, R^2 = Me
8 R = H, R^1 = Br, R^2 = Me
9 R = allyl, R^1 = H, R^2 = Ph
10 R = allyl, R^1 = H, R^2 = *p*-$NO_2C_6H_4$
11 R = H, R^1 = Br, R^2 = Ph
12 R = H, R^1 = Br, R^2 = *p*-$NO_2C_6H_4$

21

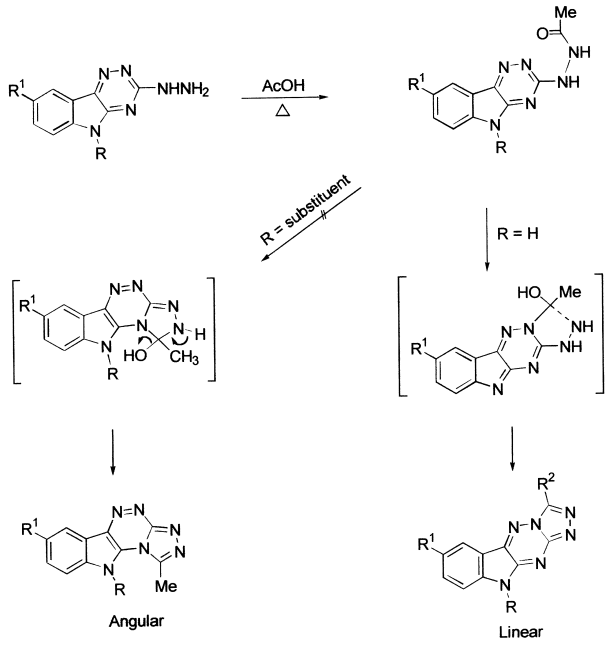
22 R = allyl, R^1 = H
23 R = H, R^1 = Br

24

15 R = allyl, R^1 = H, R^2 = Me
16 R = H, R^1 = Br, R^2 = Me
17 R = allyl, R^1 = H, R^2 = Ph
18 R = allyl, R^1 = H, R^2 = *p*-$NO_2C_6H_4$
19 R = H, R^1 = Br, R^2 = Ph
20 R = H, R^1 = Br, R^2 = *p*-$NO_2C_6H_4$

13 R = allyl, R^1 = H
14 R = H, R^1 = Br

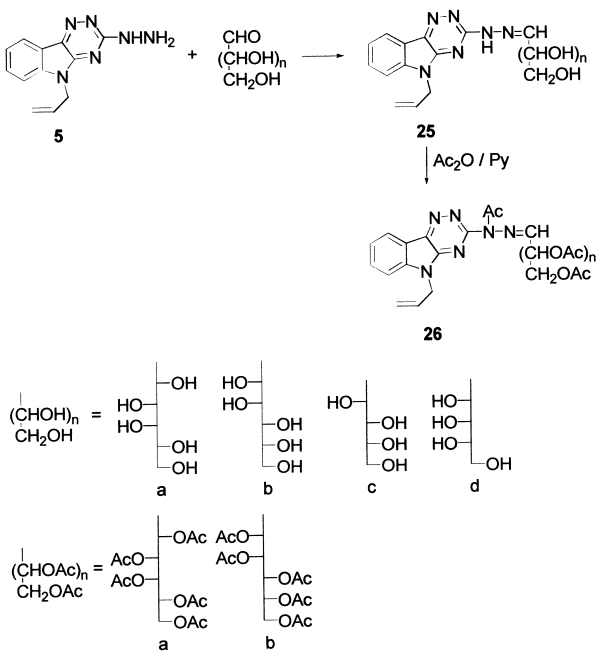
Scheme 1



Angular

Linear

Scheme 2



5

25

26

Scheme 3

Schemes: 3

Tables: 1

References: 27

Techniques used: IR, 1H NMR

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References cited in this synopsis

1 E.S.H. El Ashry, N. Rashed, M. Taha, and E. Ramadan, *Adv. Heterocycl. Chem*., 1994, **59**, 39.
2 E.S.H. El Ashry, N. Rashed, M. Taha, and E. Ramadan, *Adv. Heterocycl. Chem*., 1994, **61**, 207.
3 H. Neunhoeffer, *Heterocyclic Compounds*, Ed. by A. Weissberger, E. C. Taylor, 1978, **33**, 1.
4 H. Neunhoeffer, *Comprehensive Heterocyclic Chemistry*, (A.J. Boulton and A.Mc. Killop, eds), **3**, 385.
21 A. Mousaad, H. Abdel Hamid, A. El Nemr, and E. S. H. El Ashry, *Bull. Chem. Soc. Jpn*., 1992, **65**, 546.
22 N. Rashed, A. El Nemr, and E.S.H. El Ashry, *Spectroscopy Lett*., 1993, **26**, 1817.
23 A. Mousaad, N. Rashed, E. Ramadan, and E.S.H. El Ashry, *Spectroscopy Lett*., 1994, **27**, 677.
24 N. Rashed, M. Shoukry, and E.S.H. El Ashry, *Bull. Chem. Soc. Jpn*., 1994, **67**, 149.
25 N. Rashed, H. Abdel Hamid, E. Ramadan, and E. S. H. El Ashry, *Nucleosides Nucleotides*, 1998, **17**, 1373.
26 E.S.H. El Ashry, N. Rashed, H. Abdel Hamid, and E. Ramadan, *Z. Naturforsch*, 1997, **52b**, 873.
27 Allen & Hanbury's Ltd., Neth. Pat., 6,410,823; *Chem. Abstr*., 1965, **63**, 13 295.