NEW SYNTHESES OF 4(5)-ARYL-5(4)-(2-CHROMONYL)-1,2,3-TRIAZOLES FROM 2-STYRYLCHROMONES AND SODIUM AZIDE

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Abstract - The reactions of 2-α-bromostyrylchromones or 2-styrylchromones with sodium azide afforded 4(5)-aryl-5(4)-(2-chromonyl)-1,2,3-triazoles. In the case of 2-α-bromostyrylchromones, the unexpected 1-aryl-5-(2-chromonylmethyl)tetrazoles have been obtained as minor products and the mechanism of its formation is discussed. The bromination/dehydrobromination reactions of 2-styrylchromones were also studied.

1,2,3-Triazoles are well known five-membered nitrogen heterocyclic compounds with numerous applications in organic synthesis, as well as in industrial, pharmaceutical and agrochemical areas, and with extensive biological activities.[1]

The importance of 1,2,3-triazoles has encouraged an intensive search for synthetic strategies.[1,2] One of the most important methods is based on the thermal 1,3-dipolar cycloaddition of azides to alkynes. A wide range of substituents can be incorporated both into the alkyne and azide components providing a flexible approach to 1-substituted 1*H*-1,2,3-triazoles. 1,2,3-Triazoles unsubstituted at the nitrogen atoms have been obtained either by the direct addition of hydrazoic acid to alkynes or by using sodium azide in the presence of an acid, both procedures being somewhat dangerous. The use of trimethylsilyl azide as

dipole and the subsequent removal of the silyl group provide a much safer procedure.[3] The cycloaddition of azides to alkenes is a general route for 1,2,3-triazolines.[1,2,4] In some cases an *in situ* aromatization into 1,2,3-triazoles takes place but most of them lose nitrogen below 100°C. This lability causes low yields and/or preparative difficulties in the reactions performed at high temperature. These cycloadditions are also usually sluggish, only cycloalkenes and compounds with "activated" double bonds such as quinones, enamines and enol ethers have shown higher reactivity. However, it has been reported that some azide ion-catalysed intramolecular cycloadditions of vinyl azides provide 1,2,3-triazoles in a single step.[1,5] Synthesis of 1,2,3-triazoles by the reaction of sodium azide with vinyl bromides having electron-withdrawing substituents has also been demonstrated.[6]

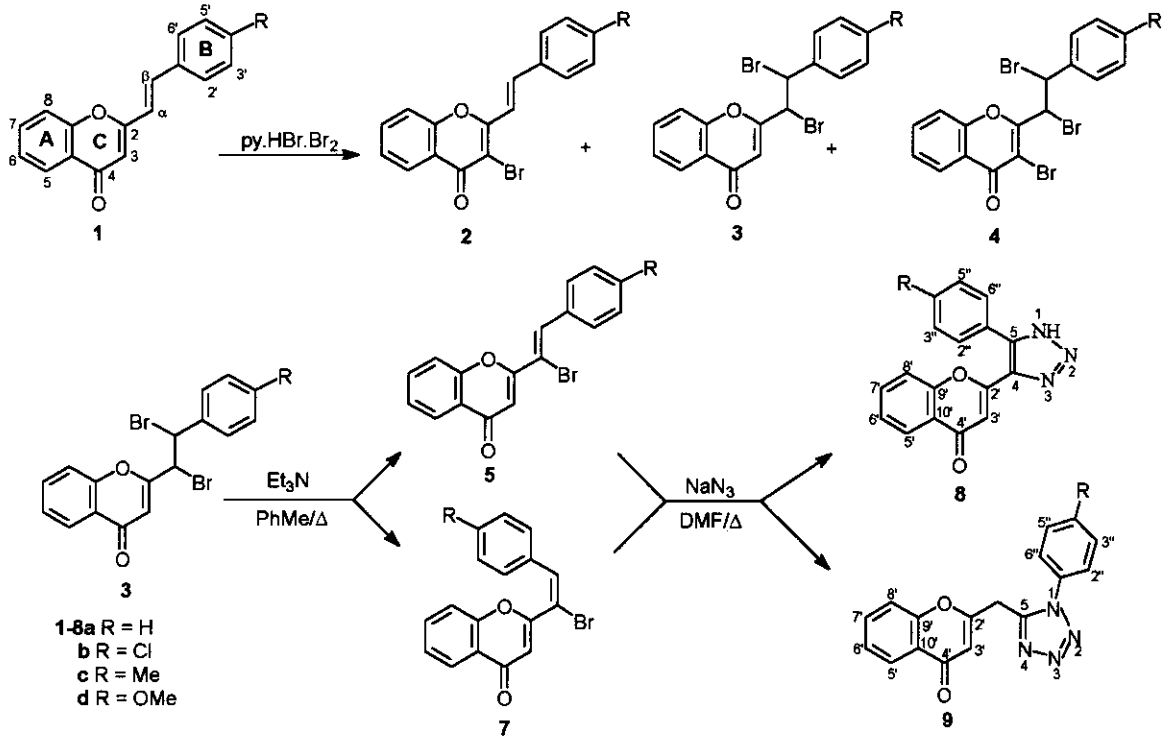
The importance of 1,2,3-triazoles and our continuing interest in the chemistry of 2-styrylchromones[7] prompted us to launch a program to prepare 1,2,3-triazoles from 2-styrylchromones.

Our first synthetic approach is based on the reaction of 2-α-bromostyrylchromones with sodium azide. To prepare the desired starting materials, 2-styrylchromone (**1a**) was treated with pyridinium tribromide (1 equiv.) in acetic acid at room temperature. Preparative TLC of the mixture obtained afforded 3-bromo-2-styrylchromone (**2a**), 2-(1,2-dibromo-2-phenylethyl)chromone (**3a**) and 3-bromo-2-(1,2-dibromo-2-phenylethyl)chromone (**4a**) in low yield and poor mass balance (~ 40%) (Scheme 1). By using two molar equivalents of pyridinium tribromide, followed by silica gel column chromatography, only two brominated products (**3a**) (44%) and (**4a**) (41%) were obtained. When this procedure was applied to 2-styrylchromones (**1b,c**), the dibrominated chromones (**3b,c**) and tribrominated compounds (**4b,c**) were obtained in good yields. In contrast, the bromination of 4'-methoxy-2-styrylchromone (**1d**) failed to give the expected product (**3d**), but instead the 3-bromo-4'-methoxy-2-styrylchromone (**2d**) (10%), 4'-methoxy-2-α-bromostyrylchromone (**5d**) (32%) and 2,3-dibromo-2-(1,2-dibromo-2-phenylethyl)-4-chromanone (**6d**)[8] (22%) were the products obtained.

When 2-(1,2-dibromo-2-phenylethyl)chromones (**3a-c**) were subjected to dehydrobromination using triethylamine in refluxing toluene, both geometric isomers (*Z*)-2-α-bromostyrylchromones (**5a-c**) and

(*E*)-2-α-bromostyrylchromones (**7a-c**)[9] were obtained, the more stable (*Z*)-isomers (65-81%) being the major products in each case (Scheme 1).

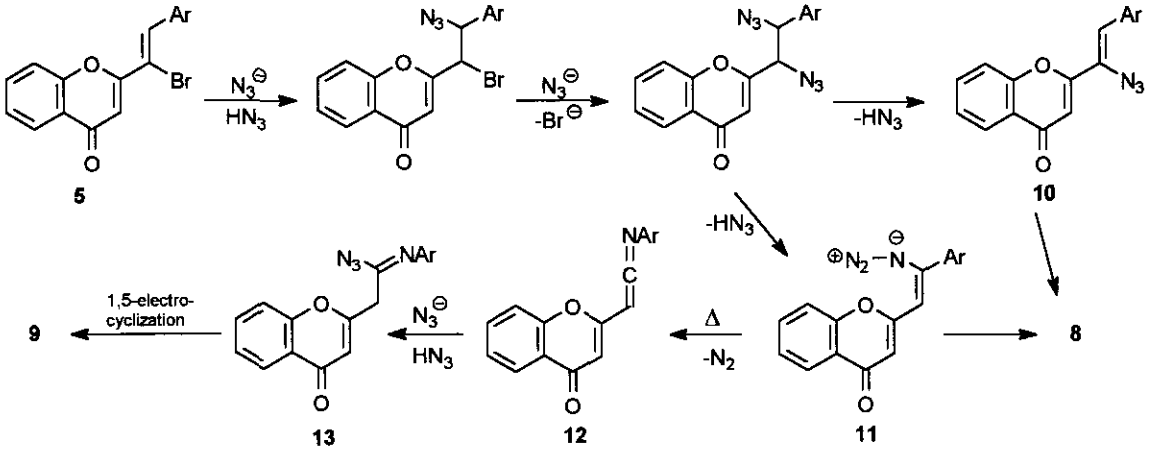
Treatment of (*Z*)-2-α-bromostyrylchromones (**5a,b**) with an excess of sodium azide in refluxing DMF, followed by acidic work-up and preparative TLC, afforded 4(5)-aryl-5(4)-(2-chromonyl)-1,2,3-triazoles (**8a,b**)[10,11] (38-40%) and 1-aryl-5-(2-chromonylmethyl)tetrazoles (**9a,b**)[12] (10-12%) (Scheme 1). The same products, triazole (**8a**) (30%) and tetrazole (**9a**) (10%), were obtained from (*E*)-2-α-bromostyryl-chromone (**7a**) under the same conditions.



Scheme 1

To explain the formation of products (**8**) and (**9**), the transformation of bromides (**5**) into α- and β-azido-vinyl compounds (**10**) and (**11**) in the well-documented addition-substitution-elimination pathway[5b] seems likely (Scheme 2). Both **10** and **11** may cyclize to the triazoles (**8**) but β-vinyl azides (**11**) can also give

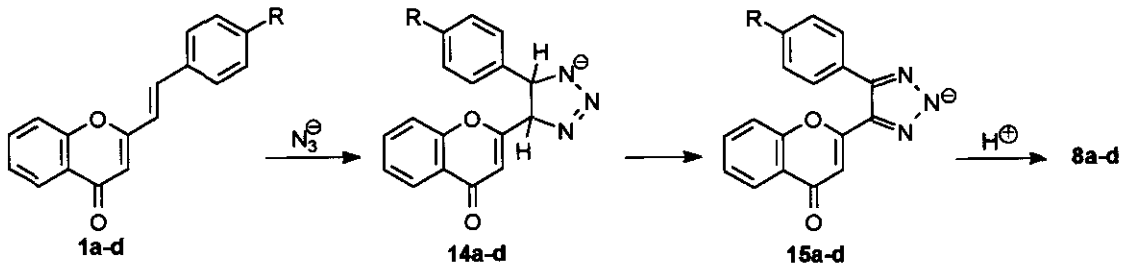
ketene imines (**12**) by loss of nitrogen and a subsequent aryl migration. Conjugate addition to ketene imines (**12**) results in the formation of imino azides (**13**) which then provide tetrazoles (**9**) by an 1,5-electrocyclization (Scheme 2), a proposal which has been put forward in other situations.[5c,13]



Scheme 2

To avoid the bromination/debromination steps in the conversion of 2-styrylchromones (**1**) into triazoles (**8**), we decided to study the reaction of chromones (**1a-d**) with sodium azide, in refluxing DMF, aiming to prepare 1,2,3-triazolines to be further oxidised to the corresponding 1,2,3-triazoles. Surprisingly, the reactions of 2-styrylchromones (**1a-d**) with sodium azide, followed by acidic treatment, directly gave 4(5)-aryl-5(4)-(2-chromonyl)-1,2,3-triazoles (**8a-d**)[11] in acceptable yields (48-59%) (Scheme 3). A mechanism that is consistent with the 1,2,3-triazoles (**8a-d**) formation involves not only the addition of the azide ion and cyclization but also the spontaneous oxidation of the formed 1,2,3-triazoline anions (**14**) to the 4(5)-aryl-5(4)-(2-chromonyl)-1,2,3-triazole anions (**15**). This aromatization of anions (**14**) can be explained by the formation of the very stable aromatic system (**15**). The addition of the azide ion to the double bond of 2-styrylchromones (**1**) can be envisaged as occurring in one of two different ways: i) by a concerted 1,3-dipolar cycloaddition of the azide ion as an anionic dipolar system, to the double bond of

1;[4] ii) by a nucleophilic addition to the β-position of 2-styrylchromones (**1**), followed by 1,5-dipolar cycloaddition of the resulting species.[3]



Scheme 3

In summary, we developed two new synthetic methods for the preparation of the hitherto unknown 4(5)-aryl-5(4)-(2-chromonyl)-1,2,3-triazoles from readily available 2-styrylchromones.

ACKNOWLEDGEMENTS

Thanks are due to the University of Aveiro and FCT-Portugal, for funding the Research Unit 62/94, to the Hungarian Scientific Research Fund (OTKA # T22290) and also to the Portuguese-Hungarian Intergovernmental Science and Technology Cooperation Programme (Project 423/OMFB/SCIAE//P-2/96).

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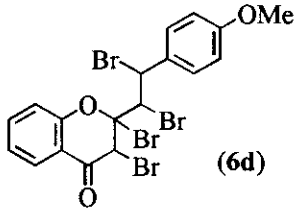
8. The structure of 2,3-dibromo-2-(1,2-dibromo-2-phenylethyl)-4-chromanone (**6d**) is as follows:



(6d)

9. Most characteristic ^{1}H and ^{13}C NMR resonances of isomers (*Z*)- and (*E*)-2-α-bromostyrylchromones (**5**) and (**7**): **5a-c**, δ (ppm) 8.05-8.11 (H-β) and 133.9-135.2 (C-β); **7a-c**, 7.41-7.46 (H-β) and 135.2-138.7 (C-β). Due to the non-coplanarity between the B ring and the other part of the molecule in the (*E*)-isomers (**7a-c**), H-β is shielded and C-β deshielded relatively to the (*Z*)-isomers (**5a-c**).

10. Although each one of the described 4(5)-aryl-5(4)-(2-chromonyl)-1,2,3-triazoles (**8a-d**) is a mixture of tautomers, only one is depicted in the numbering for the ^{13}C NMR assignments.

11. Characterisation of 4(5)-phenyl-5(4)-(2-chromonyl)-1,2,3-triazole (**8a**) as an example of the set of compounds (**8**): mp 225-227°C; ^{1}H NMR (DMSO-d_6+TFA) δ 6.78 (s, 1H, H-3'), 7.17 (d, 1H, H-8', J = 8.4 Hz), 7.45 (dd, 1H, H-6', J = 7.2 and 7.8 Hz), 7.52 -7.54 (m, 3H, H-3",4",5"), 7.68-7.76 (m, 3H, H-2",6",7'), 8.03 (dd, 1H, H-5', J = 1.3 and 7.8 Hz); ^{13}C NMR (DMSO-d_6+TFA) δ 108.4

(C-3'), 118.1 (C-8'), 124.0 (C-10'), 125.2 (C-5'), 125.9 (C-6'), 128.5 (C-1"), 128.7 (C-3",5"), 129.5 (C-2",6"), 129.8 (C-4"), 134.6 (C-7'), 135.4 (C-5), 142.1 (C-4), 155.7 (C-9'), 157.8 (C-2'), 176.8 (C-4'); MS *m/z* (rel. int.) 289 ($M^{+\bullet}$, 30), 288 (100), 272 (9), 261 (8), 233 (10), 204 (9), 169 (12), 140 (8), 121 (28), 120 (12), 114 (11), 92 (26). *Anal.* Calcd for $C_{17}H_{11}N_3O_2$: C , 70.58; H, 3.83; N, 14.53. Found: C, 70.71; H, 3.83; N, 14.30.

12. Characterisation of 1-phenyl-5-(2-chromonylmethyl)tetrazole (**9a**) as an example of the set of compounds (**9**): mp 149-150°C; ^{1}H NMR ($CDCl_3$) δ 5.57 (s, 2H, CH_2), 6.18 (s, 1H, H-3'), 7.34 (d, 1H, H-8', J = 8.1 Hz), 7.43 (ddd, 1H, H-6', J = 0.8, 7.6 and 7.8 Hz), 7.55 -7.63 (m, 3H, H-3",4",5"), 7.69 (ddd, 1H, H-7', J = 1.6, 7.6 and 8.1 Hz), 7.73 (dd, 2H, H-2",6", J = 1.7 and 7.9 Hz), 8.15 (dd, 1H, H-5', J = 1.6 and 7.8 Hz); ^{13}C NMR ($CDCl_3$) δ 48.9 (CH_2), 111.3 (C-3'), 117.9 (C-8'), 123.0 (C-10'), 123.6 (C-1"), 125.88 (C-5'), 125.94 (C-6'), 128.8 (C-2",6"), 129.6 (C-3",5"), 131.9 (C-4"), 134.4 (C-7'), 155.2 (C-5), 155.9 (C-9'), 159.2 (C-2'), 177.2 (C-4'); MS *m/z* (rel. int.) 304 ($M^{+\bullet}$, 55), 276 (12), 275 (11), 262 (42), 249 (25), 248 (58), 247 (36), 220 (16), 219 (13), 173 (12), 159 (20), 146 (54), 132 (25), 131 (100), 129 (26), 118 (28), 105 (25), 104 (20), 103 (32), 92 (35), 89 (51). *Anal.* Calcd for $C_{17}H_{12}N_4O_2$: C , 67.10; H, 3.97; N, 18.41. Found: C, 67.51; H, 4.25; N, 18.01.

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Received, 9th November, 1998