Synthetic approaches towards [1]benzopyrano [4,3-*b*]thieno[2,3-*e*]pyridines via intramolecular Diels-Alder reactions of 1,2,4-triazines

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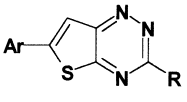
Efficient syntheses are reported of [1]benzopyrano[4,3-*b*]thieno[2,3-*e*]pyridines (**20**), by the application of an intramolecular Diels–Alder reaction employing the intermediate appropriately designed functionalised thieno [3,2-*e*][1,2,4]triazines.

Keywords: fused thiophenes, fused pyridines, fused benzopyrans, intramolecular Diels-Alder reactions

Much attention has been directed towards the synthesis and applications of different isomeric thienopyridines. Among such applications of this class of compound are their uses for the preparation of doped conducting polymers useful for electrodes, displays and electromagnetic shields.[1] Some derivatives showed interesting therapeutic applications as antiglaucoma agents,[2] anticonvulsants,[3] calcium channel modulators,[4] and others have been tested for use in the therapy of arterial thrombotic disorders.[5] Other biological applications have been reported.[6]

1,2,4-Triazines have been extensively used as electron-deficient dienes for the preparation of pyridine derivatives through their reaction with electron rich dienophiles by the application of Diels–Alder cycloaddition reactions with inverse electron demand.[7] Recently, we have developed procedures for the synthesis of the isomeric thieno[2,3-*e*][1,2,4]triazines **1** and thieno[3,2-*e*][1,2,4]triazines **2**.[8,9] We report here some of our results directed towards the utility of derivatives of **1** and **2** as potential starting materials for the synthesis of novel thienopyridines of potential useful application. Our approaches depend on the application of inter- as well as intra-molecular cycloaddition reactions of **1** and **2** with different dienophilic reagents. In the present work we describe our first successful applications of the intramolecular Diels–Alder reaction for the synthesis of thienopyridines via the intermediate thieno[3,2-*e*][1,2,4]triazines.



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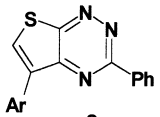
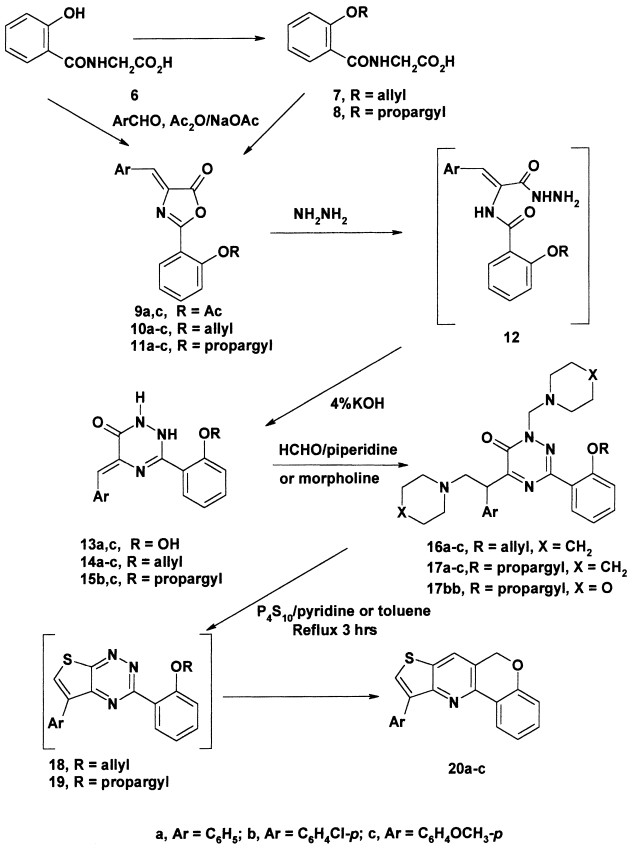


2

In the present investigation we have achieved a successful and efficient synthesis of [1]benzopyrano[4,3-*b*]thieno[2,3-*e*]pyridines **20a-c**, which constitute an interesting new ring system of fused thieno[3,2-*b*]pyridines with benzo[*b*]pyran. Scheme 2 illustrates our synthetic approach towards compounds **20**. Thus, salicuric acid **6** was alkylated with allyl bromide and propargyl bromide to give the corresponding *o*-allyloxy- and *o*-propargyloxybenzoylglycines **7, 8**. Condensation of each of **6–8** with the appropriate aromatic aldehydes in acetic anhydride and sodium acetate gave the corresponding oxazolone derivatives **9-11**. The latter were reacted with hydrazine hydrate to give the corresponding hydrazides **12** which were converted *in situ* upon heating with 4% KOH to the corresponding triazin-6-ones **13–15**. Mannich reaction of **14a–c, 15a–c** with piperidine or morpholine and formaldehyde in methanol gave the corresponding bis-Mannich bases **16a–c, 17a–c, 17bb**. Heating **16a–c** with phosphorus pentasulfide in pyridine gave 30–40% of the corresponding thienopyridines **20a–c**. On the other hand, similar treatment of each of compounds **17** gave only 5–10% of the corresponding **20a–c** along with a mixture of other unidentifiable products. Changing the reaction time (3–10 hours) did not improve the yield in the latter cases.



Scheme 2

In our first attempts we prepared compounds **13** as starting materials for the preparation of the corresponding allyl or propargyl derivatives **14, 15** via alkylation. However, attempts to alkylate compounds **13a–c** with allyl and propargyl halides in different basic media under variety of conditions did not lead to an adequate yield of the desired products **14, 15**. We therefore started with compounds **7, 8** to prepare directly the required starting triazines **14, 15**.

The formation of the new thienopyridines **20a–c** proceeds as illustrated in Scheme 3. Thus, thiation of the Manich bases **16**, **17** leads to the corresponding 6-mercapto-5-vinyl-1,2,4-triazines **21** as reported recently.[9] The latter then undergoes intramolecular cyclisation to give **22** which aromatises by loss of H_2 to give the corresponding thienotriazines **18, 19**. These

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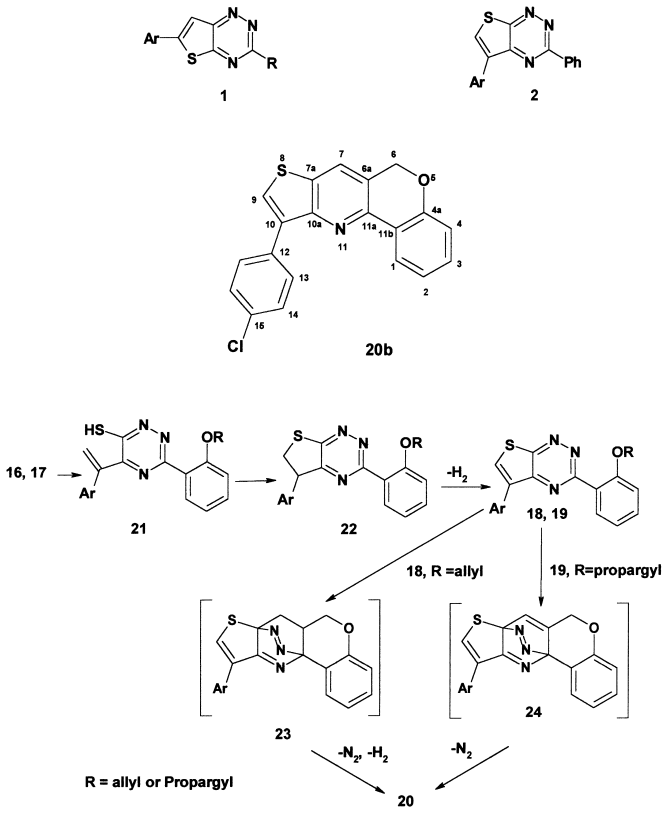
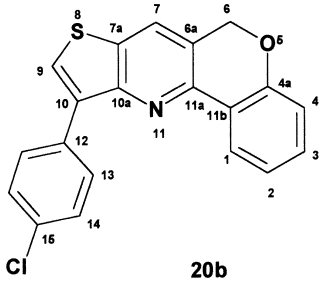


Scheme 3

undergo intramolecular 4 + 2 cycloaddition to give the intermediates **23**, **24** which lose nitrogen (and H_2 in case of **23**) to give the final products **20**.

The structure of the new thienopyridines was confirmed by ^{1}H NMR and ^{13}C NMR spectroscopy. Full proton and carbon NMR signals assignment of the new **20b** (Ar = *p*-ClC_6H_4) derivative was achieved using different 1D and 2D-NMR techniques including H,H-COSY, NOE-difference, DEPT, HMQC and HMBC experiments. Thus, from ^{1}H NMR, H-6 was readily assigned at δ 5.37 (s, 2H). By irradiation at H-6 from NOE-difference experiment H-7 was assigned at δ 7.96 (showed highest NOE enhancement) and the thiophene H-9 appears at 7.84 (s, 1H). From these assignments and H,H-COSY, other protons were readily assigned by examining the different cross peaks. Thus, H-1, H-2, H-3, H-4 were assigned at δ 8.37 (dd, 1H), 7.17 (dt, 1H), 7.37 (dt, 1H), 7.03 (dd, 1H) respectively. The *p*-chlorophenyl protons H-13, H-14 were assigned at δ 8.11 (d, 2H) and 7.52 (d, 2H) respectively. From decoupled ^{13}C NMR, DEPT-CH, HMQC and HMBC the different carbon signals of **20b** were assigned at δ 68.8 (C-6), 126.9 (C-9), 134.0 (C-10), 153.3 (C-10a), 147.1 (C-11a), 123.9 (C-11b), 125.5 (C-1), 122.9 (C-2), 131.8 (C-3), 117.5 (C-4), 157.0 (C-4a), 122.9 (C-6a), 127.4 (C-7), 136.0 (C-7a), 133.3 (C-12), 130.2 (C-13), 129.0 (C-14), 133.4 (C-15).



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Techniques used: IR, NMR (^{1}H, ^{13}C, H,H-COSY, NOE-difference, DEPT, HMQC and HMBC) and MS.

Schemes: 3

References: 10

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