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Synthesis of pyrazolo[4′,3′:3,4]pyrido[1,2-*a*]benzimidazoles and related new ring systems by tandem cyclisation of *vic*-alkynylpyrazole-4-carbaldehydes with (het)aryl-1,2-diamines and investigation of their optical properties

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ABSTRACT

The synthesis of 2*H*- and 3*H*-pyrazolo[4′,3′:3,4]pyrido[1,2-*a*]benzimidazole derivatives from 3-alkynyl- or 5-alkynylpyrazole-4-carbaldehydes and benzene-1,2-diamines was carried out using copper-free tandem cyclisation. When 2,3-diaminopyridine was used as the diamine component in this type of tandem cyclisation, 3*H*-pyrazolo[4,3-*c*]imidazo[1,2-*a*:5,4-*b*′]dipyridine derivatives were obtained. Copper catalysis and microwave activation were required for the reaction of 5-alkynylpyrazole-4-carbaldehydes and 1,8-naphthalenediamine, affording the corresponding 13,13a-dihydro-3*H*-pyrazolo[4′,3′:3,4]pyrido[1,2-*a*]perimidines. The structure assignments were based on data from ^{1}H, ^{13}C and ^{15}N spectroscopy and single-crystal X-ray diffraction analyses. The optical properties of the obtained new heterocyclic derivatives were studied by UV–vis and fluorescence spectroscopy.

1. Introduction

It is widely accepted that the pyrazole system is an important substructure of many biologically active substances, including several drug molecules and agrochemicals currently on the market.[1–5] This is particularly true for condensed pyrazoles,[6] of which the PDE5-inhibitor Sildenafil is a well-known example.[7] In addition, fused heterocyclic systems such as dipyrazolo[3,4-*b*:3′,4′-*d*]pyridines exhibit strong fluorescence and have been applied in the preparation of blue light-emitting diodes.[8] Thus, heterocyclic systems possessing pyrazole nuclei are of interest to medicinal chemists and materials scientists, and their synthesis is a worthwhile task.

In a series of recent publications, we have shown that pyrazole-4-carbaldehydes containing alkynyl functional groups adjacent to the formyl moiety are valuable starting materials for the construction of condensed pyrazole systems. These include, for instance, pyrano[4,3-*c*]pyrazol-4(1*H*)-ones and -4(2*H*)-ones, 1,5- and 2,5-dihydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-ones, pyrazolo[4,3-*c*]pyridines and dipyrazolo[1,5-*a*:4,3-*c*]pyridines.[9–13] In continuation of this program, which is devoted to exploiting the synthetic potential of these building blocks, we present a simple method for the synthesis of 2*H*- and 3*H*-pyrazolo[4′,3′:3,4]pyrido[1,2-*a*]benzimidazole, 3*H*-pyrazolo[4,3-*c*]imidazo[1,2-*a*:5,4-*b*′]dipyridine and 13,13a-dihydro-3*H*-pyrazolo[4′,3′:3,4]pyrido[1,2-*a*]perimidine derivatives. These compounds represent previously unknown tetracyclic and pentacyclic *N*-containing heterocyclic systems.

2. Results and discussion

2.1. Chemistry

The synthesis strategy for the construction of the 3*H*-pyrazolo[4′,3′:3,4]pyrido[1,2-*a*]benzimidazole ring system was based on the tandem cyclisation of *vic*-alkynylpyrazole-4-carbaldehydes with benzene-1,2-diamines, as outlined in Scheme 1. Recently, either the addition of 2-arylbenzimidazoles to alkynyl bromides followed by Pd-catalysed intramolecular C–H vinylation or Rh-catalysed intramolecular oxidative cross-coupling of 1-styrylbenzimidazoles has been employed for the construction of the benzimidazo[2,1-*a*]isoquinoline ring system, which is the benzo analogue of the

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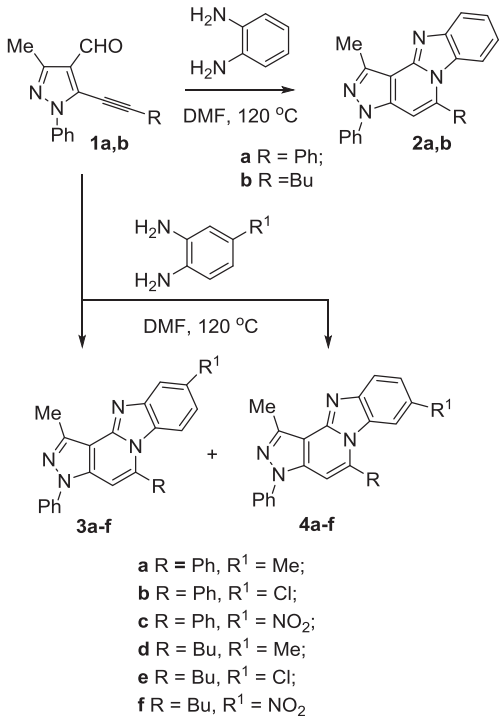
aforementioned ring system.[14,15] However, since the commonly used method for obtaining benzimidazo[2,1-*a*]isoquinoline derivatives consists of reacting 2-alkynylbenzaldehydes with 1,2-phenylenediamines under different reaction conditions, several variants such as microwave-accelerated tandem processes, silver(I) catalysed tandem reactions in water and iodocyclisations have been applied.[16–21]

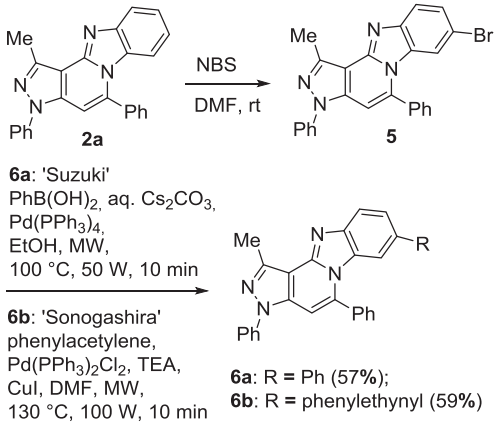


Scheme 1. Construction of the 3*H*-pyrazolo[4′,3′:3,4]pyrido[1,2-*a*]benzimidazole ring system.

Therefore, a related approach was conceived for the construction of the target 3*H*-pyrazolo[4′,3′:3,4]pyrido[1,2-*a*]benzimidazole ring system. The synthesis of the starting 5-alkynylpyrazole-4-carbaldehydes **1a**,**b** was accomplished via Sonogashira coupling of the corresponding 5-chloropyrazole-4-carbaldehydes.[9] In order to find the optimal conditions for the tandem cyclisation, the starting material **1a** was first reacted with benzene-1,2-diamine in DMSO under metal-free conditions or in the presence of a CuI catalyst with either conventional heating or microwave irradiation.[18] However, in all cases, the reaction gave a complex mixture of products containing only traces of the desired cyclisation product **2a**. In contrast, changing the reaction solvent to DMF dramatically enhanced the yield of **2a** to 90% without any need for the CuI catalyst. The reaction of **1b** with benzene-1,2-diamine under analogous conditions afforded compound **2b** in 79% yield. DMSO may have been an inadequate solvent under the applied reaction conditions due to its oxidising properties,[22,23] whereas one of the starting materials, namely—benzene-1,2-diamine is very sensitive to the oxidation.[24]

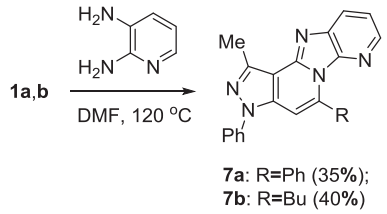
With the optimal conditions in hand, the scope of the reaction was assessed by reacting pyrazole-4-carbaldehydes **1a**,**b** with 4-methyl-, 4-chloro- and 4-nitrobenzene-1,2-diamines. In principle, the use of 'asymmetric' benzene-1,2-diamines can lead to regioisomeric reaction products (**3a**–**f** and **4a**–**f**, respectively). The results obtained with precursor **1a** demonstrated that the use of benzene-1,2-diamines with either electron-donating or electron-withdrawing groups in most cases gave good to acceptable yields of the target tetracycles **3a**–**c**, whereas the isomeric compounds **4a**–**c** were not isolated using this method. However, the reaction of **1b** with 4-methylbenzene-1,2-diamine provided regioisomers **3d** and **4d** (ratio 1:0.55) as an inseparable mixture in 70% total yield. Surprisingly, in the case of the reaction of 4-chlorobenzene-1,2-diamine with **1b**, the corresponding 9-chloro derivative **3e** was obtained only in 60% yield, whereas employment of 4-nitrobenzene-1,2-diamine gave the 8-nitro derivative **4f** as the sole isolated product in 65% yield. Only trace amounts of the other regioisomers (**4e** and **3f**, respectively) could be detected in the reaction mixture.

We also explored the further functionalisation of tetracycle **2a** (Scheme 2). Treatment of **2a** with NBS in DMF at room temperature gave the bromo derivative **5**. The attachment of the bromine atom at position 8 was fully shown by careful NMR spectroscopic analysis. The ability of the bromine atom in **5** to participate in palladium-catalysed cross-coupling reactions was proven by the Suzuki-type reaction of **5** with phenylboronic acid, which afforded compound **6a** in 57% yield. This coupling was carried out at 100 °C under microwave irradiation in EtOH using $Pd(PPh_3)_4$ as the catalyst and aq Cs_2CO_3 as base. Microwave-assisted Sonogashira reaction conditions ($Pd(PPh_3)_2Cl_2$, CuI and triethylamine at 130 °C and 100 W for 10 min) were applied for the cross-coupling of **5** with phenylacetylene. The reaction proceeded smoothly to afford compound **6b** in 59% yield (Scheme 2).



Scheme 2. Synthesis and cross-coupling reactions of compound **5**.

When 2,3-diaminopyridine was used as the diamine component in the reaction with precursors **1a**,**b**, the reaction provided the 3*H*-pyrazolo[4,3-*c*]imidazo[1,2-*a*:5,4-*b*′]dipyridine derivatives **7a**,**b** (Scheme 3). In principle, the formation of two isomeric structures occurred in this reaction due to the different position of the pyridine nitrogen in the ring system plane. However, only regioisomers **7a**,**b** were isolated from the complex reaction mixture, with low yields of 35% and 40%, respectively.



Scheme 3. Construction of the 3*H*-pyrazolo[4,3-*c*]imidazo[1,2-*a*:5,4-*b*′]dipyridine ring system.

The reaction between the carbaldehydes **9a**,**b** and benzene-1,2-diamines was also explored (Scheme 4). The starting compound **9a** was obtained from 1-phenyl-3-trifloyloxypyrazole-4-carbaldehyde (**8**) according to the procedure we have previously described.[25] In an analogous approach, the previously unknown starting material **9b** resulted from the reaction of **8** with 1-hexyne. Again, the