Pyridazines. Part 35:[1] Traceless Solid Phase Synthesis of 4,5- and 5,6-Diaryl-3(2*H*)-pyridazinones

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Abstract: A new method for the traceless solid phase synthesis of 3(2*H*)-pyridazinones has been developed employing dihydropyran-functionalized resin. The procedure has permitted the preparation of several diarylpyridazinones through a Suzuki cross-coupling reaction and cleavage conditions that promoted a retro-ene fragmentation.

Key words: solid phase, pyridazinone, ene-adducts, palladium

The high speed synthesis of organic molecules, and in particular the synthesis of heterocyclic compounds, by solid phase or solution phase methods is rapidly becoming established as an enabling technology in modern medicinal chemistry.[2] An important objective in solid phase organic synthesis (SPOS) is the development of chemistries applicable to combinatorial techniques that are not limited by the tether and where target molecules can be efficiently cleaved from the resin by a specialized reagent or transformation. However, the need for the attachment of substrates onto solid supports through the use of linkers inevitably leaves behind molecular vestiges upon cleavage. The biological activity of compounds made in this way could be altered due to the presence of these molecular appendages. In an attempt to circumvent this problem, traceless linkers and cyclization cleavage procedures have been introduced.[3] The pyridazine nucleus and its 3-oxo derivatives [3(2*H*)-pyridazinones] have been recognized as versatile pharmacophores in medicinal chemistry and they show a wide range of biological actions.[4] Curiously, only a few studies on the SPOS of pyridazine derivatives have been described[5] and, therefore, the development of convenient, versatile and efficient solid phase routes to access chemical libraries of these compounds is highly desirable.

As part of our efforts aimed towards the preparation and biological evaluation of pyridazine derivatives,[6–8] we wish to describe here our studies that have identified a highly efficient and versatile traceless solid phase route to prepare chemical libraries of 4,5- and 5,6-substituted-3(2*H*)-pyridazinones amenable to automated high-speed parallel synthesis.

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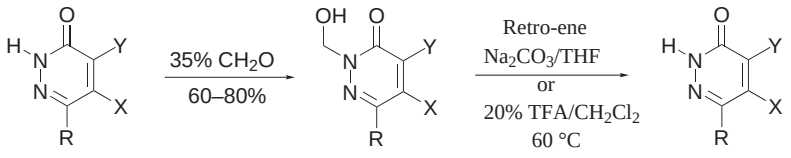
Several works on palladium-catalyzed reactions have shown that these transformations represent a powerful tool to perform pharmacomodulation in the pyridazinone series[9,10] and, for this reason, we became interested in developing a solid-phase route to carry out these kinds of transformations. One key aspect has guided our design strategy: to perform palladium-catalyzed reactions on pyridazinones it is necessary to protect the NH-group since the acidic nature of the lactam functionality of this group usually interferes with the transformations.[10] Bearing this point in mind, for the solid phase chemistry it is important to select a suitable scaffold and linker combination that is able not only to attach the pyridazinone ring onto the solid support but also to protect the heterocycle at the same time. The most obvious approach to carry out a traceless solid phase 3(2*H*)-pyridazinone synthesis would be to use the pyridazinone N–H as a resin attachment point, which could subsequently be cleaved to give the free 3(2*H*)-pyridazinone. There have, however, not been any reports in the literature of such a strategy being successfully accomplished. Although one can envisage attaching the 3(2*H*)-pyridazinone unit to directly onto Merrifield resin by a simple alkylation, there are several problems associated with this direct approach. Firstly, even in typical solution chemistry there are several protecting groups at position 2 that are sometimes difficult to remove.

Taking into account the aspects described above, we designed a general traceless approach to generate disubstituted-3(2*H*)-pyridazinone libraries in the solid phase by using the Ellman's resin. The first results of this project allow to prepare diaryl-3(2*H*)-pyridazinones **6** and **7** and are represented in this paper. Compounds **6** and **7** are structurally related to the well documented cyclo-oxygenase-2 inhibitors.[11] To compliment these objectives we chose as reactive scaffolds the 2-hydroxymethylhalopyridazinones **2**,[12] which can be prepared in excellent yields by refluxing **1** in 35% formaldehyde solution (Scheme 1). One of these compounds (**1a**) have been successfully used recently by our group as reactive intermediates in palladium-catalyzed transformations.[13] Compounds **2** are 1-O, 3-N, 5-O ene adducts[14] that lose formaldehyde in a retro-ene transformation catalyzed by the action of bases and/or heat. In our previous attempts to adapt this chemistry onto the solid support we observed that this retro-ene transformation can also be promoted in almost quantitative yield by the conditions usually employed to remove the substrates form the solid support (20% TFA/CH_2Cl_2 solution, 50 °C, 12 h, Scheme 1).

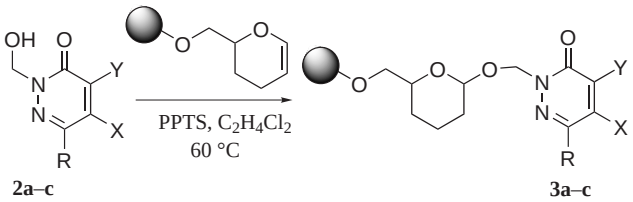


1a–c **2a–c** **1a–c**

a) R = Ph, Y = H, X = Br, b) R = H, Y = Cl, X = Cl, c) R = H, Y = Br , X = Br

Scheme 1

The solid phase synthesis of 4,5- and 5,6-diaryl pyridazinones **6** and **7** is achieved through the previous preparation of immobilized 5-halo- and 4,5-dihalopyridazinones **2**. Alcohols **2** are attached to Ellman's DHP-linked polystyrene resin (Aldrich) using PPTS in 1,2-dichloroethane (Scheme 2).[15] This operation was repeated twice to ensure quantitative conversion of **2** to **3**. The progress of the reaction was qualitatively monitored by IR spectroscopy by following the appearance of the carbonyl band of the heterocyclic ring (1660–1670 cm^{-1}). Similar transformations but starting from the 3(2*H*)-pyridazinones **1a–c** allow to obtain the corresponding supported derivatives but only in low yields.



2a–c **3a–c**

a) R = Ph, Y = H, X = Br, b) R = H, Y = Br, X = Br
c) R = H, Y = Cl, X = Cl

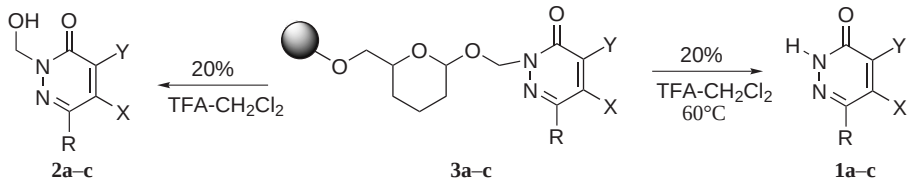
Scheme 2

The coupling efficiency was determined by mass balance after cleavage of the material from the support (Scheme 3). These methods allowed us to isolate, depending on the conditions, the 2-hydroxymethyl-pyridazinones **2** using the traditional cleavage conditions (20% TFA/CH_2Cl_2, r.t., 15 min) or the 3(2*H*)-pyridazinones **1** by heating the mixture (20% TFA/CH_2Cl_2) at 50 °C during 12 hours (Scheme 3). It is important to point out that in order to isolate compounds **2** as pure samples one must employ short reaction times (15–20 min) for the cleavage process.

Isolation of compounds **1** under cleavage conditions can be rationalised in terms of the initially formed 2-hydroxymethyl-3-pyridazinones **2** losing formaldehyde in a second step, which can be recognized as a retro-ene fragmentation. Although we focused our attention on the direct preparation of 3(2*H*)-pyridazinones, these results are particularly important since such conditions could permit the introduction of a new point of diversity, at position 2 of the heterocyclic system, in the chemical libraries prepared by this methodology.

We next turned our attention to the introduction of aryl groups in **3** by following the well established palladium-catalyzed Suzuki approach (Scheme 4).[16] Thus, treatment of **3** with an excess of the appropriate aryl boronic acid (2.5 equiv per reactive halogen), a catalytic amount of $Pd(PPh_3)_4$ (0.05 equiv) and 2 M Na_2CO_3 as base in dichloroethane at 80 °C (12 h), provided the expected arylated immobilized 3-pyridazinones **4** and **5**.[17] In order to avoid submitting the resin to the harsh cleavage conditions (50 °C, 12 h), the desired products **6** and **7** were cleaved from the resin using 20% TFA/ CH_2Cl_2 (15 min) and the cleavage solutions were subsequently heated at 50 °C during 10 hours.[18]

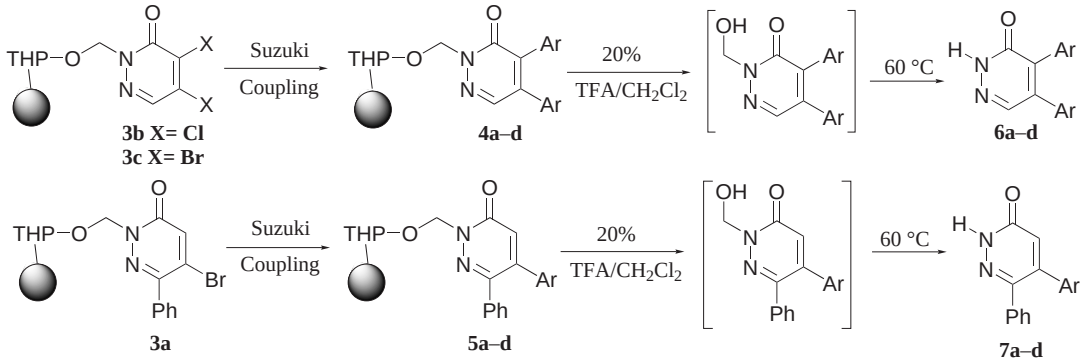
As expected, the acetal linkage was totally stable to the conditions of the Suzuki coupling (2 M Na_2CO_3, 70 °C) and we did not observe cleavage of the heterocycle from the support. Arylpyridazinones **6** and **7** were obtained in 74–86%[19] yield and 80–96% purity, as determined by HPLC.[20] Complete characterization of the compounds obtained was performed by the analytical and spectroscopic methods (MS, IR and NMR experiments) and by comparing the data with those of authentic samples previously prepared by us (Table 1).[9,12]



2a–c **3a–c** **1a–c**

a) R = Ph, Y = H, X = Br, b) R = H, Y = Br, X = Br
c) R = H, Y = Cl, X = Cl

Scheme 3



a) Ar = Ph, b) Ar = 4-CH_3-Ph, c) Ar = 4-CH_3O-Ph, d) Ar = 4-Cl-Ph

Scheme 4

Table 1 Diaryl-3(2*H*)-pyridazinones Prepared

Compound	Ar	Yield (%)[a]	Purity (%)[b]
6a	Ph	86	80
6b	4-CH_3Ph	83	83
6c	4-OCH_3Ph	80	81
6d	4-ClPh	79	85
7a	Ph	81	93
7b	4-CH_3Ph	80	96
7c	4-OCH_3Ph	76	91
7d	4-ClPh	74	93

[a] Yields of crude product based on experimentally determined loading of Ellman's resin-bound alcohol.
[b] Purity of the compounds was based on the integration area from HPLC traces of crude products (254 nm UV detection).

In summary, we have developed a novel and efficient solid phase synthesis of 4,5- and 5,6-diaryl-3(2*H*)-pyridazinones following a Suzuki-type C–C coupling reaction assisted by a retro-ene transformation. This procedure is the first example of a traceless solid phase synthesis of pyridazinones. The results of further studies on the scope and generality of this and other palladium-mediated solid phase strategies for the synthesis of libraries of pyridazinones will be reported in due course.

Acknowledgment

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(12) Selected physical and spectroscopic data of representative compounds **2**. Compound **2a**: Yield: 89%, mp 237–238 °C. IR (KBr): 3100, 1680 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.55–7.47 (m, 5 H, Ph), 7.40 (s, 1 H, CH), 5.58 (d, *J* = 8.1 Hz, 2 H, CH_2), 4.74 (t, *J* = 8.1 Hz, 1 H, OH). Compound **2b**: Yield: 70%, mp 113–114 °C. IR (KBr): 3400, 2960, 1670 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): 8.19 (s, 1 H, CH), 6.97 (t, *J* = 7.6 Hz, 1 H, OH), 5.34 (d, *J* = 7.6 Hz, 2 H, CH_2).
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(15) **General Procedure for the Preparation of Immobilized Pyridazinones 3:** The amount of 300 mg of Ellman's resin (Aldrich, 0.420 mmol) was loaded into a reactor on a PLS 6 × 4 organic synthesizer (Advanced ChemTech) and treated with **2** (1.26 mmol), PPTS (0.63 mmol) and dichloroethane (4 mL). The mixture was heated at 70 °C during 12 h, drained, washed sequentially with dichloroethane (3 × 5 mL), CH_2Cl_2 (3 × 5 mL), DMF (3 × 5 mL), CH_2Cl_2 (3 × 5 mL), MeOH (3 × 5 mL), Et_2O (3 × 5 mL) and dried in a vacuum dessicator.

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(17) **General Procedure for Suzuki Arylation of Immobilized Halopyridazinones 3:** The amount of 100 mg of pyridazinone-derivatized support **3** (0.120 mmol) was loaded into a reactor on a PLS 6 × 4 organic synthesizer (Advanced ChemTech) and treated with the appropriate boronic acid (0.300 mmol for **1a** and 0.600 mmol for **1b**,**c**), $Pd(PPh_3)_4$ (0.05 equiv), 2 M Na_2CO_3 (0.7 mL) and DME (3 mL). The mixture was heated at 70 °C during 12 h, drained, washed sequentially with DME (3 × 5 mL), DME/H_2O (3 × 5 mL), 0.2 N HCl (3 × 5 mL), EtOAc (3 × 5 mL), MeOH (3 × 5 mL), Et_2O (3 × 5 mL) and dried in a vacuum dessicator.

(18) **General Procedure for Cleveage of 4,5- and 5,6-Diarylpyridazinones Form Solid Support:** The above resin (75 mg) was treated with 20% TFA in CH_2Cl_2 (2 mL) for 15 min. After filtration and washing with CH_2Cl_2 the combined filtrates were heated at 50 °C for 12 h, concentrated to give a residue wich was re-dissolved in a 1:1 mixture of CH_3CN–H_2O. The solvent was then removed under presure to give pyridazinones **6** and **7**.

(19) Selected physical and spectroscopic data of compounds **6** and **7**: Compound **6a**: Mp 135–136 °C. IR (KBr): 3100–2600, 1642 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ = 13.05 (br s, 1 H, NH), 7.74 (s, 1 H, CH), 7.04–6.92 (m, 10 H, Ph). Compound **6b**: Mp 147–149 °C. IR (KBr): 3100–2600, 1639 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ = 13.16 (br s, 1 H, NH), 7.90 (s, 1 H, CH), 7.52–7.00 (m, 8 H, Ph), 2.24 (s, 6 H, 2 × CH_3). Compound **7a**: Mp178–180 °C. IR (KBr): 3100–2600, 1668, 1589 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ = 11.58 (br s, 1 H, NH), 7.38–7.20 (m, 10 H, Ph), 7.01 (s, 1 H, CH). Compound **7b**: Mp 198–200 °C. IR (KBr): 3100–2600, 1642 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ = 11.40 (br s, 1 H, NH), 7.41–7.29 (m, 5 H, Ph), 7.18 (d, *J* = 8.0, 2 H, phenyl), 7.07 (d, *J* = 8.0, 2 H, phenyl), 7.01 (s, 1 H, CH), 2.33 (s, 3 H, CH_3).

(20) HPLC analyses were performed using a 5 μm 4.6 × 150 mm reverse phase column (70% acetonitrile/30% H_2O) over 40 min, flow rate 0.5 mL/min.