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# Pyridazines. Part 34: Retro-ene-assisted palladium-catalyzed synthesis of 4,5-disubstituted-3(2*H*)-pyridazinones☆

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**Abstract**—The efficient one-pot bis-functionalization of the 4,5-positions of the 3-pyridazinone ring has been performed using Suzuki, Sonogashira and Stille cross-coupling reactions assisted by a retro-ene fragmentation. This route allows access in a shorter synthetic sequence to several pharmacologically useful 3(2*H*)-pyridazinones. 

The interesting pharmacological activities shown by pyridazine derivatives have recently attracted the attention of several research groups from academia and industry.[2] The useful nature of pyridazinones has stimulated the search for new synthetic approaches to achieve substitution on these electron-deficient rings. In particular, special interest has been directed to palladium cross-coupling reactions and several excellent palladium-assisted procedures have been described for the synthesis of both pyridazines and pyridazinones.[3] Previous papers on this topic have illustrated how these transformations represent a powerful tool to perform pharmacomodulation in the pyridazinone series and, for this reason, we became interested in developing a short yet highly versatile route to prepare 4,5-substituted-3(2*H*)-pyridazinones. One key aspect has guided this new design strategy: to perform palladium-catalyzed reactions on pyridazinones it is necessary to protect the N*H* group since the acidic nature of the lactam functionality usually interferes with the required transformations.

A survey of the literature on protecting groups revealed that methods for the protection of the amide or lactam functionality are limited.[4] There is a dearth of new protecting groups and/or reagents that are able to undergo deprotection under mild conditions and new developments in this area are therefore of great interest. The use of methoxymethyl (MOM) or benzyloxymethyl (BOM) groups has recently been reported as a convenient method for protection during these transformations.[5] Furthermore, the use of Lewis acids (aluminum chloride and boron tribromide) to perform the mild and selective deprotection of 2-substituted-3-pyridazinones bearing acid-sensitive functionalities has also been reported.[5c,6] As part of our ongoing medicinal chemistry program aimed at obtaining novel pyridazinone-based antiplatelet agents,[7] it was decided to prepare several 4,5-substituted-3(2*H*)-pyridazinones **3a**–**e**. A number of 4,5-diaryl-2-methyl-3-pyridazinones that are structurally related to **3** have recently been described by Lemiére et al.[8]

In order to prepare compounds **3**, which have a free NH group, it was necessary to develop a short synthetic strategy that avoided the use of previously described 2-blocked pyridazinones (such as 2-benzyl-, 2-benzyloxymethyl- or 2-methoxymethyl-3-pyridazinones). In these cases deprotection after the coupling reaction requires hydrogenolysis or treatment with refluxing HCl or Lewis acids. The ultimate aim of this study was to find a new, simple, more convenient and labile protecting group that can be easily removed under coupling conditions. We describe here the rapid, efficient and convenient one-pot synthesis of 4,5-substituted 3-(2*H*)-pyridazinones **3** starting from the readily obtainable 4,5-dihalo-2-hydroxymethyl-3(2*H*)-pyridazinones **2**.

Compounds **2** were obtained in satisfactory yields by refluxing the corresponding 3(2*H*)-pyridazinone **1** in 35% formaldehyde solution (Scheme 1).[9,10] The relatively easy preparation of these compounds is a valu-

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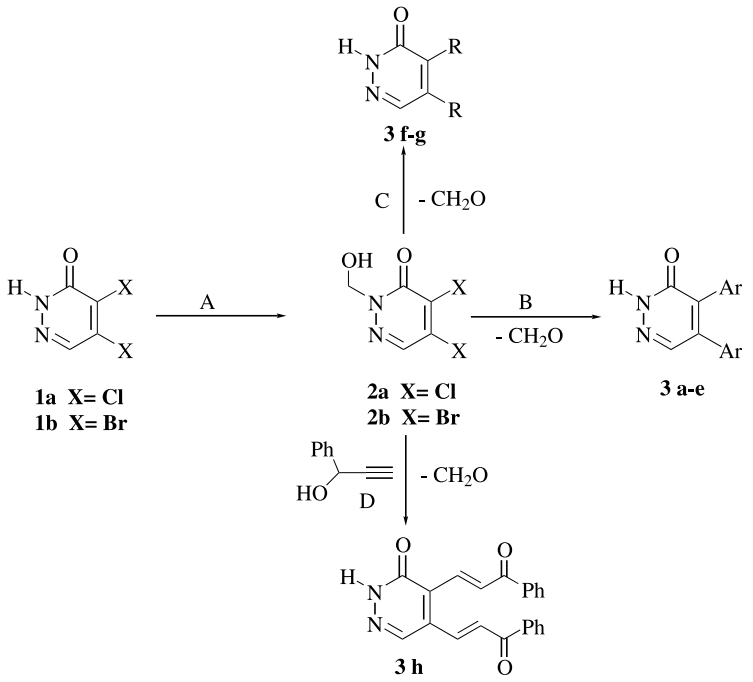



**Scheme 1.** *Reagents and conditions*: (A) $CH_2O$, reflux; (B) $ArB(OH)_2$, $Pd(PPh_3)_4$, $Na_2CO_3$, $DME/H_2O$, reflux; (C) organotin, $Pd(Ph_3)_2Cl_2$, toluene, reflux; (D) CuI, $Pd(Ph_3)_2Cl_2$, DMF, 55°C.

able aspect of this synthetic route. However, the most noteworthy advantage regarding their synthetic applicability as 2-blocked pyridazinones in cross-coupling reactions is derived from their chemical and thermal stability. These compounds are 1-O, 3-N, 5-O ene-adducts[11] that readily lose formaldehyde through a retro-ene reaction promoted by a base and/or by heat.

Once position 2 had been blocked it was possible to study the palladium-catalyzed reactions on **2** (Scheme 1). The first reaction studied was the bis-Suzuki arylation of **2**, which required the presence of a base in the reaction medium. The transformation was carried out by heating under reflux a mixture of **2** and 2.5 equiv. of the appropriate boronic acid under Suzuki conditions[12] (Scheme 1).

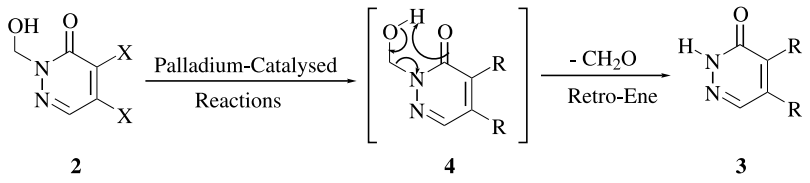
The Suzuki bis-arylation of **2a** or **2b** gave the 4,5-diaryl-3(2*H*)-pyridazinones **3a**–**e** in high yields after 12–24 h (Table 1).[13,16] Similarly, Stille coupling of **2b** using the appropriate reagents and conditions (Scheme 1) led to the expected 4,5-substituted-3(2*H*)-pyridazinones **3f**–**g** in excellent yields (Table 1).[14,16] In accordance with previous results,[15] the Sonogashira coupling of 1-phenyl-2-propyn-1-ol with **2b** afforded the 4,5-bis[*E*-(3-oxo-3-phenylpropenyl)]-3(2*H*)-pyridazinone **3h**[14] (Scheme 1), most probably due to the base-promoted isomerization of the 4,5-bis(3-hydroxy-3-phenyl-prop-1-ynyl)-3(2*H*)-pyridazinone intermediate.[15]

**Table 1.** Suzuki arylation of **2a**. Physical data of compounds **3**[16]

| Compound | R | Method | Yield (%) | Mp (°C) |
|---|---|---|---|---|
| **3a** | Phenyl | A | 86 | 135–136 |
| **3b** | 4-$CH_3$-Phenyl | A | 90 | 147–149 |
| **3c** | 4-Cl-Phenyl | A | 78 | 156–158 |
| **3d** | 4-$OCH_3$-Phenyl | A | 92 | 141–143 |
| **3e** | 4-$N(CH_3)_2$-Phenyl | A | 90 | 139–140 |
| **3f** | $COCH_3$ | B | 82 | 145–146 |
| **3g** | $CH{=}CH_2$ | B | 78 | 135–135 |
| **3h** | CH=CHCOPh | C | 85 | 189–191 |

As expected, all of the above transformations occur with exclusive formation of 3(2*H*)-pyridazinones **3** regardless of whether the reaction conditions involve the use of base or not. These results confirm that the retro-ene reaction operating in these examples can be promoted by heat. The fact that 3(2*H*)-pyridazinones **1** are not reactive under these conditions indicates that the first step of these transformations most probably involves the bis-palladium-catalyzed cross-coupling reaction of **2** to afford a 4,5-substituted ene adduct **4**, which was not isolated (Scheme 2). In the second step this intermediate loses formaldehyde to give **3** in a transformation that may be regarded as a retro-ene fragmentation promoted either by heat or the basic medium required to perform the Suzuki or Sonogashira reaction.

In summary, a practical and efficient procedure has been developed for the preparation of 4,5-substituted-3(2*H*)-pyridazinones using 2-hydroxymethyl-4,5-dihalo-3-pyridazinones as reactive intermediates. This one-pot transformation is based on a base- and/or heat-promoted retro-ene fragmentation. These results demonstrate the synthetic utility of the 2-hydroxymethyl unit




2 4 3

**Scheme 2.**

as a convenient protecting group for the lactam function in pyridazinone chemistry. The procedure is superior to existing processes and has allowed access to several pharmacologically useful pyridazinones through a short, high yielding synthetic sequence.

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10. Representative procedure for the preparation of compounds **2**. A mixture of **1** (4.3 mmol) and 35% formaldehyde (34 mL, 43 mmol) was flushed with argon for 5 min. The suspension was stirred and heated under reflux (oil bath 110°C) under argon until the starting material had been consumed. The mixture was cooled and the suspension was concentrated to dryness under reduced pressure. The resulting solid was purified by column chromatography on silica gel (AcOEt/hexane, 1:2). Physical and spectral data for compounds **2**: **2a**: Yield: 70%, mp 111–112°C. IR (KBr): 3400, 3100, 1670 $cm^{-1}$. $^1H$ NMR (dimethyl sulfoxide-$d_6$, 300 MHz): 8.19 (s, 1H, CH), 6.97 (t, $J=7.6$ Hz, 1H, OH), 5.34 (d, $J=7.6$ Hz, 2H, $CH_2$). $^{13}C$ NMR ($CDCl_3$, 300 MHz): 155.9, 136.8, 136.2, 133.6, 74.9. **2b**: Yield: 65%, mp 138–140°C. IR (KBr): 3100–3000, 1668 $cm^{-1}$. $^1H$ NMR (dimethyl sulfoxide-$d_6$, 300 MHz): 8.13 (s, 1H, CH), 6.93 (t, $J=7.3$ Hz, 1H, OH), 5.33 (d, $J=7.3$ Hz, 2H, $CH_2$). $^{13}C$ NMR ($CDCl_3$, 300 MHz): 156.24, 137.8, 131.5, 130.6, 75.1.
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13. Representative procedure for bis-Suzuki arylations on compounds **2**. A mixture of **2** (1.6 mmol), arylboronic acid (4 mmol), $Pd(PPh_3)_4$ (0.032 mmol) and $Na_2CO_3$ (0.67 g, 6.4 mmol) in 3:1 DME/$H_2O$ (18 mL) was flushed with argon for 5 min. The mixture was stirred and heated under reflux (oil bath 120°C) under argon until the starting material had been consumed. The reaction mixture was cooled, the solution was concentrated to dryness under reduced pressure and the residue was purified by column chromatography on silica gel. Selected physical and spectral data for representative compounds **3**. 4,5-Diphenyl-3(2*H*)-pyridazinone (**3a**): Yield: 86%, mp 135–136°C. IR (KBr): 3100–3000, 1642 $cm^{-1}$. $^1H$ NMR (dimethyl sulfoxide-$d_6$, 300 MHz): 13.04 (bs, 1H), 7.74 (s, 1H), 7.04 (m, 6H), 6.95 (m, 4H). 4,5-Bis(4-tolyl)-3(2*H*)-pyridazinone (**3b**): Yield: 90%, mp 147–149°C. IR (KBr): 3100–2923, 1639 $cm^{-1}$. $^1H$ NMR (dimethyl sulfoxide-$d_6$, 300 MHz): 13.16 (bs, 1H), 7.90 (s, 1H), 7.24–7.00 (m, 8H), 2.24 (s, 6H). 4,5-Bis-(4-chlorophenyl)-3(2*H*)-pyridazinone (**3c**): Yield: 78%, mp 156–158°C. IR (KBr): 3500–2924, 1642 $cm^{-1}$. $^1H$ NMR (dimethyl sulfoxide-$d_6$, 300 MHz): 13.20 (bs, 1H), 7.96 (s, 1H), 7.64–7.31 (m, 4H), 7.28–6.99 (m, 4H).
14. Selected physical and spectral data for representative compounds **3**. 4,5-Diacetyl-3(2*H*)-pyridazinone (**3f**). Yield: 82%, mp 189–191°C. IR (KBr): 3100–2958, 1690, 1678 $cm^{-1}$. $^1H$ NMR (dimethyl sulfoxide-$d_6$, 300 MHz): 12.25 (s, 1H), 8.12 (s, 1H), 2.45 (s, 3H), 2.42 (s, 3H). 4,5-Bis-[*E*-(3-oxo-3-phenylpropenyl)]-3(2*H*)-pyridazinone

(**3h**): Yield: 85%, mp 145–146°C. IR (KBr): 3150–3000, 1695, 1668 $cm^{-1}$. $^1H$ NMR (dimethyl sulfoxide-$d_6$, 300 MHz): 12.89 (s, 1H), 8.09 (s, 1H), 7.89–7.34 (m, 12H), 7.10 (d, $J=16.3$ Hz, 1H), 7.04 (d, $J=15.2$ Hz, 1H).

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16. Complete details of the synthesis, spectral characteristics and biological evaluation of the compounds obtained will be published elsewhere in a full paper. All compounds gave satisfactory microanalytical data (C, H, N±0.4%) and spectral data ($^1H$, $^{13}C$, FTIR, MS). Yields given correspond to isolated pure compounds.