Pyridazines. Part 30:[1] Palladium-Catalysed Synthesis of 5-Substituted 6-Phenyl-3(2*H*)-pyridazinones Asissted by a Retro-Ene Transformation

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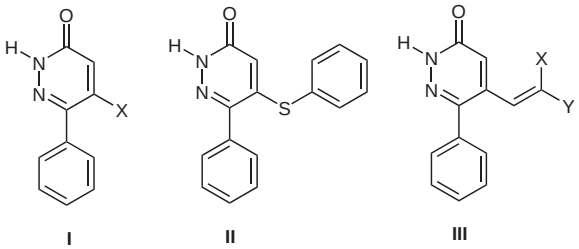
This paper is dedicated to Professor Raúl Mocelo of the University of Havana, Cuba, on the occasion of his birthday.

Abstract: The efficient one-pot functionalization, through palladium-catalysed reactions, of position 5 of the 6-phenyl-3(2*H*)-pyridazinone system has been performed using a retro-ene-assisted fragmentation. This route allows access through a short synthetic sequence to several pharmacologically useful 3(2*H*)-pyridazinones.

Key words: pyridazinone, ene-adducts, palladium, catalysis

The pyridazine nucleus and its 3-oxo derivatives [3(2*H*)-pyridazinones] are recognised as versatile pharmacophores in medicinal chemistry. Within this class of compound, 6-aryl-3(2*H*)-pyridazinones and their 4,5-dihydro derivatives have received a great deal of attention in recent years because they show a wide range of biological actions.[2] Several papers on this topic have described the pharmacological utility of these compounds[3–5] and we recently described the platelet inhibitory activity of a series of 5-substituted 6-phenyl-3(2*H*)-pyridazinones **I**.[6–8] The structural manipulation at position 5 of this system has allowed us to develop new and potent antiplatelet agents **II** and **III** (Figure 1).[1,9]

The results mentioned above have directed our project, which is concerned with the search for new pyridazinone-based antiplatelet agents, to the development of efficient synthetic procedures that allow the rapid pharmacomodulation of position 5 of this system. More specifically, we have recently focused our synthetic efforts on the palladium-catalysed cross-coupling reactions of 5-halo-3(2*H*)-pyridazinones.[10,11] and dihalopyridazines.[12]



I II III

Figure 1

Most of the literature examples on this topic refer to 2-blocked-pyridazinones, and their role is limited to blocking the enolisable carbonyl group, probably because the mesomeric or tautomeric structure of the lactam function present in 3(2*H*)-pyridazinones completely inhibits palladium-catalysed transformations.[10,11] Several works have described the use of benzyl and benzyloxymethyl groups[13] but procedures for the protection of the amide or lactam functionality are limited.[14] Thus, in the absence of protecting groups and/or reagents that are able to perform deprotection under mild conditions, new methods are needed.

We recently described the use of the methoxymethyl (MOM) group as a convenient protecting group for these transformations.[10,11] However, the strong acidic conditions required to remove the MOM group from these compounds (refluxing 6 N HCl) are not tolerated by pyridazinones with acid-sensitive functionalities. In this regard, the successful use of Lewis acids (aluminium chloride and boron tribromide) as an alternative procedure to perform the efficient and mild deprotection of 2-substituted pyridazinones has been described.[15]

As part of these studies we were interested in developing a shorter synthetic strategy that avoided the use of our previously described 2-blocked pyridazinones such as 2-methoxymethyl-3-pyridazinones[10,11] [obtained from the corresponding 3(2*H*)-pyridazinone and the highly toxic methoxymethyl chloride], which have to be deprotected after the coupling reaction. Our goal was to find a new, simple, more convenient and less toxic route to 2-blocked pyridazinones with a labile group at position 2 that could be easily removed under coupling conditions. It was envisaged that such a material could be used as a reactive starting material in palladium-catalysed reactions. We report herein a rapid, efficient and convenient one-pot synthesis of 5-substituted 6-phenyl-3-(2*H*)-pyridazinones **3** starting from 5-bromo-2-hydroxymethyl-6-phenyl-3-pyridazinone (**2**) (Scheme 1).

Compound **2** can be obtained (89%) by refluxing 5-bromo-6-phenyl-3(2*H*)-pyridazinone (**1**) in 35% formaldehyde solution.[16] The easy preparation of this compound represents a valuable advantage, although the most noteworthy aspect concerning the synthetic applicability of this compound as a 2-blocked pyridazinone in cross-coupling reactions is derived from its chemical and thermal

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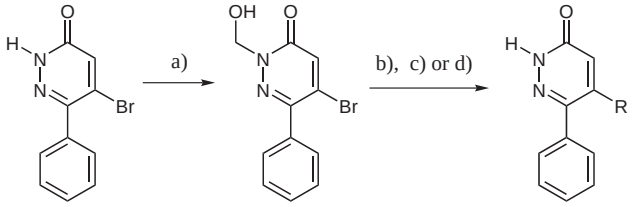

1 **2** **3**

Scheme 1 a) CH_2O/reflux, b) $ArB(OH)_2$, $Pd(PPh_3)_4$, K_2CO_3, DME–H_2O, reflux, c) alkyne, CuI, $Pd(PPh_3)_2Cl_2$, DMF, 55 °C, d) organotin, $PdCl_2(PPh_3)_2$, toluene, reflux.

stability. This compound is a 1-*O*, 3-*N*, 5-*O* ene-adduct,[17] which easily loses formaldehyde through a retro-ene reaction promoted by base and/or by heat.

Once position 2 had been blocked we proceeded to study several palladium-catalysed reactions on **2** (Scheme 1). We first examined the Suzuki arylation of **2**, which is already known to require the presence of a base in the reaction medium. The transformation was carried out by heating under reflux an equimolar mixture of **2** and the appropriate boronic acid under Suzuki conditions[18] [sodium or potassium carbonate as base, tetrakis(triphenylphosphine)palladium(0) as catalyst and a mixture of DME–water as solvent, Scheme 1]. Suzuki arylation of **2** proceeds with exclusive formation of 3(2*H*)-pyridazinones **3** in high yields after 8–24 hours (Table 1). In a similar way, Sonogashira[19] or Stille coupling of **2** using the appropriate reagents and conditions, led to the expected 5-substituted 6-phenyl-3(2*H*)-pyridazinones in high yields (Table 1)[20] regardless of whether the reaction conditions involved the use of base or not. These results confirm that the operating retro-ene reaction for these examples can be promoted by heat.

Although all of the reactions gave excellent yields (Table 1), Sonogashira couplings on **2** proved to be particularly efficient and occurred readily under mild conditions. This high reactivity is especially significant since several of the acetylene derivatives previously prepared by us were unstable under the range of conditions used to perform the cleavage of the protecting group.[15]

Since 5-bromo-6-phenyl-3(2*H*)-pyridazinone **1** is not reactive toward palladium-catalysed reactions,[10,11] the first step of these transformations most probably involves the cross-coupling reaction on **2** to afford a 5-substituted ene adduct, which was not isolated. In the second step this intermediate loses formaldehyde to give **3** in a transformation that may be regarded as a retro-ene fragmentation.

In summary, we have developed a versatile, practical and efficient one-pot palladium-catalysed procedure to prepare several 5-substituted 6-phenyl-3(2*H*)-pyridazinones **3** using the ene adduct **2** as a reactive intermediate. The use of other 2-hydroxymethylpyridazinones as precursors in several different palladium-catalysed transformations and the biological evaluation of the resulting compounds is currently under investigation.

Table 1 Palladium-catalysed Reactions on **2** and Physical data of Compounds **3**[19,20]

Compound	R	Yield (%)	Mp (°C)
3a	Ph	72	178–180
3b	4-CH_3Ph	74	198–200
3c	4-ClPh	82	222–223
3d	4-CHOPh	72	172–173
3e	C≡C–TMS	81	157–158
3f	C≡C–CH_2OH	82	200–201
3g	C≡C–$CH(OEt)_2$	88	133–135
3h	CH=CH_2	81	169–170

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(16) **Representative Procedure for Preparation of Compound 2.** A mixture of **1** (2.64 g, 0.105 mmol) and 35% formaldehyde (0.828 mL, 0.105 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 disappeared (24 h). The mixture was cooled and the suspension was concentrated to dryness under reduced pressure. The obtained solid was purified by column chromatography on silica gel (EtOAc–hexanes, 1:2). Physical and spectral data for compound **2**: Yield: 89%, mp

237–238 °C. IR (KBr): 3100–3000, 1642 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.55–7.40 (m, 5 H, Ph), 5.58 (d, *J* = 8.1 Hz, 2 H, CH_2), 4.74 (t, *J* = 8.1 Hz, 1 H, OH). ^{13}C NMR ($CDCl_3$, 300 MHz): δ = 159.6, 147.0, 134.9, 133.4, 131.7, 130.0, 129.6, 128.6, 77.1. HRMS (Autospec Micromass): *m*/*z* calcd for $C_{11}H_9BrN_2O_2$ (M^+): 279.9847. Found: 279.9859.

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(18) **Representative Procedure for Suzuki Arylations on Compound 2.** A mixture of **2** (0.45 g, 1.6 mmol), arylboronic acid (1.6 mmol), $Pd(PPh_3)_4$ (0.036 g, 0.032 mmol) and Na_2CO_3 (0.67 g, 6.4 mmol) in 18 mL of 3:1 DME–H_2O 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 disappeared. The mixture was cooled and the solution was concentrated to dryness under reduced pressure. The residue was purified by column chromatography on silica gel.

(19) **Representative Procedure for Sonogashira Couplings on Compound 2.** A mixture of **2** (0.28 g, 1.0 mmol), acetylene derivative (1.5 mmol), $Pd(PPh_3)_2Cl_2$ (0.03 g, 0.01 mmol), CuI (0.01 g, 0.01 mmol) and anhyd triethylamine (0.282 mL, 2.0 mmol) in 10 mL of DMF was flushed with argon for 5 min. The reaction mixture was stirred and heated (oil bath 55 °C) under argon until the starting material had disappeared. The reaction mixture was cooled and the solution was concentrated to dryness under reduced pressure. The residue was purified by column chromatography on silica gel.

(20) **Selected Physical and Spectral Data for Representative Compounds 3. 3a**: Yield: 90%. IR (KBr): 3100–2923, 1668, 1589 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 11.58 (br s, 1 H, NH), 7.38–7.20 (m, 10 H, phenyl), 7.01 (s, 1 H, H_4). **3b**: Yield: 78%., IR (KBr): 3500–2924, 1642 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 11.40 (br s, 1 H, NH), 7.41–7.29 (m, 5 H, phenyl), 7.18 (d, *J* = 8.0 Hz, 2 H, phenyl), 7.06 (d, *J* = 8.0 Hz, 2 H, phenyl), 7.01 (s, 1 H, H_4), 2.33 (s, 3 H, CH_3). **3c**: Yield: 78%. IR (KBr): 3500–2924, 1642 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 11.65 (br s, 1 H, NH), 7.40–7.30 (m, 5 H, Arom), 7.16 (d, *J* = 8.4 Hz, 2 H, Arom), 7.05 (d, *J* = 8.4 Hz, Arom), 6.97 (s, 1 H, H_4). **3e**: Yield: 70%. IR (KBr): δ = 3000–3100, 2136, 1654 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 12.46 (br s, 1 H), 7.73 (m, 2 H, Arom), 7.42 (m, 3 H, Arom), 7.13 (s, 1 H), 0.16 (s, 9 H, 3 × CH_3). **3f**: Yield: 86%. IR (KBr): 3100, 1680 cm^{-1}. ^1H NMR (MeOD, 300 MHz): δ = 13.18 (br s, 1 H, NH), 7.75 (m, 2 H, Arom), 7.47 (m, 3 H, Arom), 7.16 (s, 1 H, H_4), 4.35 (s, 2 H, CH_2), 3.34 (t, 1 H, *J* = 1.6 Hz, OH). **3g**: Yield: 81%. IR (KBr): 3246–2885, 2236, 1667, 1053 cm^{-1}. ^1H NMR (MeOD, 300 MHz): δ = 12.40 (br s, 1 H, NH), 7.70–7.64 (m, 2 H, Arom), 7.42–7.37 (m, 3 H, Arom), 7.17 (s, 1 H, H_4), 5.35 (s, 1 H, CH), 3.52 (m, 4 H, 2 × OCH_2), 1.15 (m, 6 H, 2 × CH_3). **3h**: Yield: 86%. IR (KBr): 1669, 1092 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 12.68 (br s, 1 H, NH), 7.43 (m, 5 H, Arom), 7.11 (s, 1 H, H_4), 6.45 (dd, 1 H, *J* = 10.9, 17.2 Hz, $CH=CH_2$), 5.87 (d, 1 H, *J* = 17.2 Hz, $CH=CH_2$), 5.50 (d, 1 H, *J* = 10.9 Hz, $CH=CH_2$).