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Sequential regio and chemoselective cross-coupling reactions by means of O^6-tri-isopropylsulfonate of 4-bromo-pyridazine 3,6-dione

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Abstract—Regioselective desymmetrization of 4-substituted pyridazin-3,6-diones using sterically hindered 2,4,6-triisopropylphenylsulfonylchloride allowed efficient sequential palladium cross-coupling reactions.

The increasing interest for pharmacologically active 6-aryl 3-aminopyridazines **3**[1–7] formally emphasizes the two critical steps allowing introduction of both the aromatic ring and the amino functions. The historical approach first involves a condensation of various arylmethylketones with commercially available α-ketoacids leading to the corresponding 6-aryl pyridazinones **1** (method a). Thus an additional activation of the resulting amide by means of $POCl_3$ afforded the corresponding chloropyridazine **2**, which was finally submitted to amination reactions.[3–7] However, the reaction did not allow rapid structural optimization of both the aryl substituents (or heteroaryl or aralkyl) and the amino substituents (NR_1R_2). As the result of the dramatic increase of palladium cross-coupling reactions (PCCR) applied to various heterocycles, that is, pyridazines, the starting 3,6-dichloropyridazines **4** constitute valuable intermediates for combining in a sequential manner both the Suzuki and amination reactions.[8–14]

The commercially available 3,6-dichloropyridazine **4a** (R = H) has been already used for that purpose.[8–13] A similar strategy was applied by our group with the easily available 4-methyl and 4-phenyl 3,6-dichloropyridazines (compounds **4b** and **4c**, respectively, method b) (see Scheme 1).

However the first step leading to substitution of **4b** and **4c** (amination or Suzuki reaction) was not regioselective, as it afforded a mixture of both regioisomers depending on the selected route (amination/Suzuki).[14] The presence of a major regioisomer (about 70% of the mixture) resulted from a clear steric hindrance effect of the substituent R. This effect was enhanced, when the nucleophile presented also some steric hindrance. Thus amination with a secondary amine (morpholine) took place on the less hindered iminochloride, and afforded a single isomer, which was further submitted to a Suzuki reaction, yielding the pure regioisomer **5**.[14]

The aim of this work was to investigate other opportunities of using the pyridazine 3,6-dione precursor **6**, but with a preliminary step of desymmetrization of amide functions, thus allowing a sequential activation of both the 3 and 6 positions of the pyridazine ring. We focused our attention on the pyridazine 3,6-diones **6**, and selected *O*-aryl sulfonates **8** as valuable leaving groups for both aminations and Suzuki reactions. Whereas the known reactivity of *O*-triflates was applied with success in PCCR involving various amide heterocycles including pyridazines,[15,16] the use of other pyridazine *O*-sulfonates may offer more versatility, and might help

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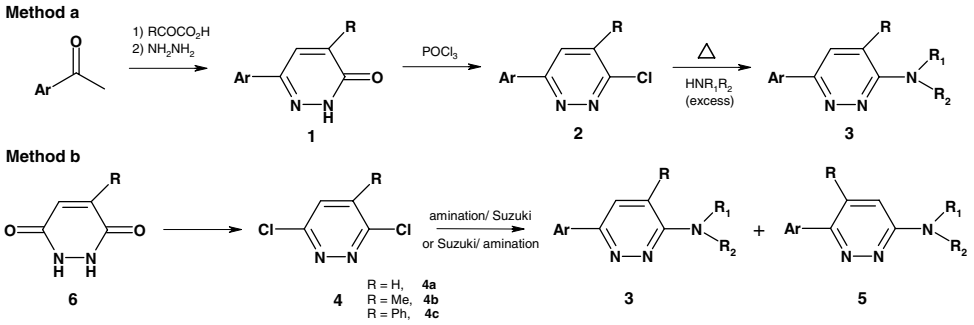


Scheme 1. Access to 4 (or 5) substituted 3-amino-6aryl pyridazine 3 (or 5).

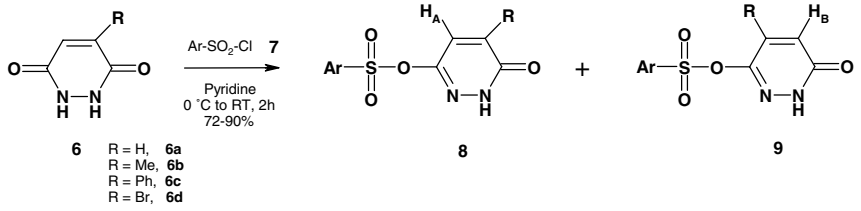
to better control regioselectivity, when the arylsulfonylchloride presents some steric hindrance. Thus a first study describes the reaction of various arylsulfonylchlorides **7** with the 4-substituted pyridazine 3,6-diones **6** (Table 1). In major cases a mixture of both regioisomers **8** and **9** were obtained. Ratio of regioisomers has been determined by ^{1}H NMR analysis (integration of H_A and H_B signals) of the pyridazine ring in the crude reaction mixture.

The position of the *O*-sulfonyl group in C-6 causes a significant downfield shift for the adjacent aromatic proton H_A in structure **8**. As found in our previous papers, significant steric effect of the R substituent yielded systematically the *O*-sulfonyl pyridazinone **8** as the major isomer.

In the *O-tosyl* series a more pronounced effect was observed with R = Ph. In all cases the major isomer could be easily recovered as a pure compound by recrystallization in ethyl acetate (entries 2–4) or cyclohexane (entries 9 and 10).[18] Structures **8b** and **9b** were assigned by NMR analysis (HMBC and NOE techniques) of the compound **10b** which was obtained from **8b** by a Suzuki reaction under μ-wave irradiation.[18]

In order to avoid any formation of the minor isomer **9**, when starting from **6**, the influence of the steric hin-

Table 1. Reaction of pyridazine 3,6-diones with various arylsulfonylchlorides



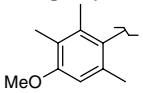
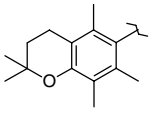
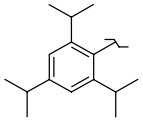
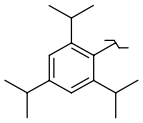
Entry	Cpds	R	Ar	Global yield (%)	**8/9** Ratio (%)	
1	**8a**	H	4Me–Ph	90		
2	**8b/9b**	Me	4Me–Ph	72	80	20
3	**8c/9c**	Ph	4Me–Ph	90	⩾90	nd
4	**8d/9d**	Br	4Me–Ph	88	70	30
5	**8e/9e**	Br	β-Naphthyl	76	80	20
6	**8f/9f**	Br	α-Naphthyl	73	85	15
7	**8g/9g**	Br		70	85	15
8	**8h/9h**	Br		73	80	20
9	**8i/9i**	Br		83	⩾95	⩽5
10	**8j/9j**	Me		90	⩾95	⩽5

Table 2. Sequential PCCR reactions with **8j**

Entry	Starting **8**	**8j** → **10**; Ar_2 (yield %)	
1	**8j**	3OMe–Ph (63)	
2	**8j**	4Cl–Ph (72)	
		8i → **11**; Ar_1 (yield %)	**11** → **12**; Ar_2 (yield %)
3	**8i**	Ph (76)	4-Cl–Ph (76)
4	**8i**	Ph (76)	3,4-DiOMe–Ph (≈48[a])
5	**8i**	4-OMe–Ph (90)	Ph (68)
6	**8i**	H_2C=CHPh (92)	3-MeO–Ph (72)

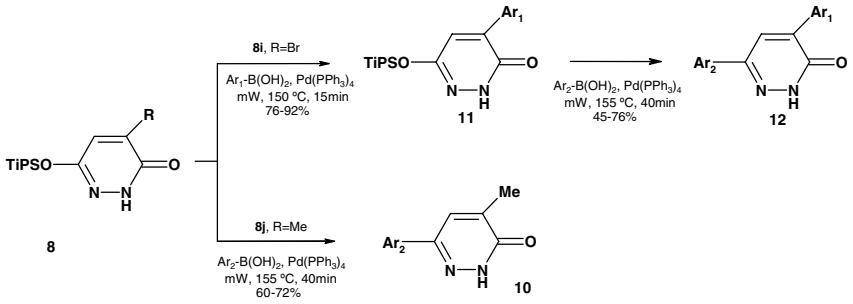
[a] Low yield due to product low solubility.

drance of the starting arylsulfonylchloride was checked. No significant modification of the ratio of regioisomers **8** and **9** was observed (Table 1, entries 4–8). However, when using the 2,4,6-triisopropyl-sulfonylchloride, the corresponding regioisomer **8** was recovered nearly pure (⩾95%, entries 9 and 10) and in good yield (83–90%). In particular, recrystallization in cyclohexane afforded the pure O^6-(2,4,6-triisopropylphenylsulfonyl) (O^6-TiPS) 4-bromo-pyridazine 3-one **8i**. This compound offers an additional anchor point for further chemical transformations (see Table 2). O^6-TiPS derivatives could be used as valuable intermediates in Suzuki reactions (entries 1 and 2 as examples) (see Scheme 2).

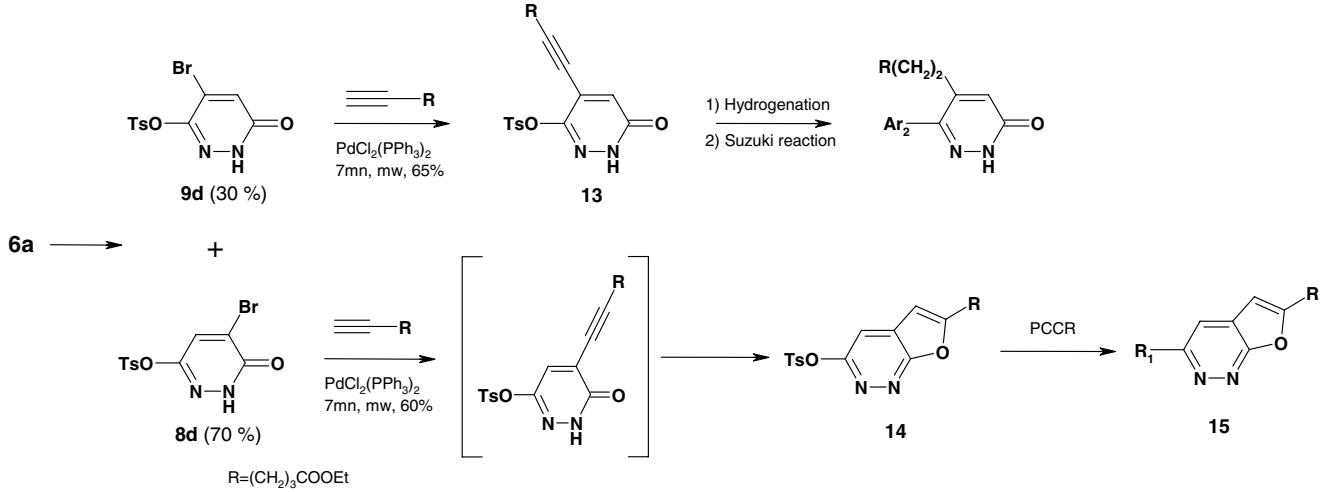
When considering the bromo intermediate **8i**, a first PCCR (Suzuki) took place regioselectively at position 4 (4-bromo more reactive than O^6-TiPS). Satisfactory yields were obtained when using microwave technologies (150 °C, 15 min).[14] A second Suzuki reaction could be performed with the resulting intermediate **11**[17] using same experimental conditions, but with a longer reaction time (155 °C, 40 min) leading to 4,6-diaryl pyridazinone **12** in satisfactory yields (Table 2, entries 3–6).

Finally the difunctionalized pyridazinone **8i** is very efficient in producing rapidly various 4,6-disubstituted pyridazinones by means of different Pd(0) coupling reactions using various catalysts, experimental conditions, and substrates (Suzuki, Sonogashira, Stille, Heck, Buchwald). However, when a Sonogashira reaction was first performed with the 4-bromo pyridazinones **8d** and **9d**, different chemical behaviours were observed.

The minor isomer **9d** gave the corresponding alkyne **13**, whereas the major isomer **8d** afforded an intermediate, which spontaneously cyclized to give the furo[2,3-*c*]pyridazine in good yield.[18] It is interesting to notice that the bi-cyclic compound **14** is ready to be further substituted, as it still contains a tosyl function (compound **15**, Scheme 3).



Scheme 2. Use of O^6-TiPS-pyridazinones in PCCR.



Scheme 3. Easy access to furo[2,3-*c*]pyridazines.

In conclusion the use of sterically hindered arylsulfonylchlorides with pyridazine 3,6-diones constitutes a simple and efficient method of activation of a less sterically hindered pyridazinone function. In particular, when starting from the 4-bromo pyridazine derivatives **8i**, the resulting O^6-TiPS derivative offers two chemically different functionalities for sequential PCCR. In addition in some cases, the Sonogashira reaction performed on the adequate regioisomer could yield novel pyridazine deriving bicyclic compounds (furo[2,3-*c*]pyridazines).

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.06.056.

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18. Supplementary data is available free of charge on the Internet at http://www.sciencedirect.com.