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A new mild synthetic route to *N*-arylated pyridazinones from aryldiazonium salts†

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An efficient method for the synthesis of *N*-arylated pyridazinones from potassium 2-furantrifluoroborate and aryldiazonium salts is described. The reaction was run in water at 0–5 °C in short reaction times and without any catalyst or additive. A mechanistic proposal is made based on the experimental data and DFT calculations.

Pyridazin-3(2*H*)-ones and their *N*-aryl substituted derivatives are building blocks found in many biologically active compounds such as pharmaceuticals and pesticides.[1] As an example, compound **1** (Fig. 1), which is used in the treatment of central nervous system disorders, a naphthalene-based compound was synthesized by copper-catalyzed *N*-arylation of pyridazinone.[2]

Several methods for the *de novo* synthesis of this kind of nitrogen heterocycles are described in the literature.[3] The most common synthetic pathways are based on the introduction of the two nitrogen atoms from hydrazine[4] and hydrazone[5] derivatives, which are sometimes prepared from aryldiazonium salts.

In an ongoing study on palladium-catalyzed cross-coupling reactions involving aryldiazonium salts and heteroaryltrifluoroborates using water as a solvent,[6] our group found that potassium 2-furantrifluoroborate did not afford the expected cross-coupling compounds when reacted with several aryldiazonium salts but rather that *N*-arylated pyridazin-3(2*H*)-one derivatives were obtained. We then tested the same reaction without the palladium catalyst and found that the same heterocycles were obtained. Therefore, we envisaged that a new simple and mild method for the preparation of *N*-arylpyridazinones could be set up directly from aryldiazonium salts and potassium 2-furantrifluoroborate under mild conditions.

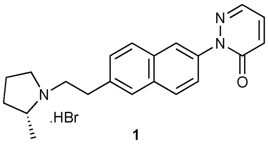

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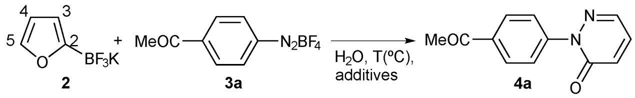
Fig. 1 Structure of *N*-aryl pyridazin-3(2*H*)-one **1**.

We first focused on the optimization of the reaction conditions using potassium 2-furantrifluoroborate **2** and *p*-acetylphenyldiazonium tetrafluoroborate **3a**. The first parameter to be evaluated was the ratio between reactants. A 53% yield of **4a** was obtained after three hours using a stoichiometric ratio (entry 1, Table 1). With an excess of aryldiazonium salt (1:2), the yield dropped to just 35% after 20 hours (entry 2, Table 1). When an excess of potassium 2-furantrifluoroborate **2** was used (2:1), the yield increased to 67% in just five minutes (entry 3, Table 1). The yield was similar (66%), although with an increased reaction time (20 minutes), when the excess of **2** was reduced to 1.2:1 and the temperature was lowered to 0–5 °C (entry 4, Table 1).

Given that we observed that the pH of the reaction medium was highly acidic at the end of the reaction, we decided to test

Table 1 Optimization of the reaction between **2** and **3a**[a]



Entry	Ratio **2**:**3a**	Reaction conditions	Yield of **4a** (%)
1	1:1	25 °C, 3 h	53
2	1:2	25 °C, 20 h	35
3	2:1	25 °C, 5 min	67
4	1.2:1	0-5 °C, 20 min	66
5	1.2:1	^{t}BuOK (5 eq.), 0–5 °C, 2 h	0
6	1.2:1	NaOAc (5 eq.), 0–5 °C, 20 min	47
7	1.2:1	NaOAc (1.2 eq.), 0–5 °C, 20 min	67

[a] Experimental procedure: **3a** dissolved in H_2O (0.107 M) was added to a stirred aqueous solution of **2** (in 6 mL of water) and the flask was protected from light.[7]

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† Electronic supplementary information (ESI) available: Experimental details, spectroscopic data and spectra of all synthesized compounds, computational details and Cartesian coordinates of all optimized stationary points. See DOI: 10.1039/c4cc03190c

the effect of adding a base.[8] The addition of an excess of ^{t}BuOK resulted in decomposition (entry 5, Table 1) so, a weaker base such as NaOAc was then tested and a 47% yield of **4a** was obtained (entry 6, Table 1). Using only 1.2 eq. of NaOAc, the yield was the same as that obtained without the base (compare entries 4 and 7, Table 1). We therefore concluded that the base was not required. When the reaction was run in solvents other than water such as ethanol or acetonitrile, a wide range of undesired and undefined products were detected. But when water was added to the organic media (EtOH : H_2O (3 : 7) and $CH_3CN : H_2O$ (3 : 7)) the product was obtained although with a slightly decreased yield, showing that water is necessary for such a process. As a last set of experiments, *in situ* generation of the aryldiazonium salt was tested. Neither by using mixtures of HBF_4–$NaNO_2$, HCl–$NaNO_2$, ^{t}BuONO nor with ^{t}BuONO–CH_3SO_3H did the results improve. Only low yields of pyridazinone and decomposition products were obtained.

Therefore, the reaction conditions of entry 4 were used to study the scope of the reaction. Both electronic and steric effects were evaluated in the aryldiazonium salt partner (Chart 1). When the diazonium salt had an electron-withdrawing substituent, pyridazinone **4** was obtained more efficiently in a shorter reaction time. With an NO_2 substituent, either in the *para* or *ortho* position, the reaction gave good yields in just five minutes (**4b** and **4c**). As the electron-donating nature of the substituent increased, the reaction time lengthened lowering the yield of the pyridazinone derivative (**4d–4j**). In an attempt to improve the yields of **4g** and **4j**, the reaction was warmed to room temperature and left for 24 hours affording a 42% yield for **4g** and 29% for **4j**. The effect of an added base (5 eq. of NaOAc) was tested in the case of **4j** without any improvement in yield being obtained. In the case of *o*-Me, **4h**, both the electronic nature of the substituent and steric hindrance had an important effect on the process. A low yield was obtained, which could not be improved by increasing the reaction time. More challenging aryldiazonium salts were then tested. As potassium naphthyldiazoniumtetrafluoroborate was unstable, the corresponding hexafluorophosphate salt was prepared and reacted resulting in moderate yields of the corresponding pyridazinone **4k**. The heteroaromatic thiophendiazonium salt also reacted affording a 32% yield of *N*-heteroarylpyridazinone **4l**. The scale up of the process was also successful since starting with 0.5 g (2.14 mmols) of **3a** the yield of **4a** was 56%.

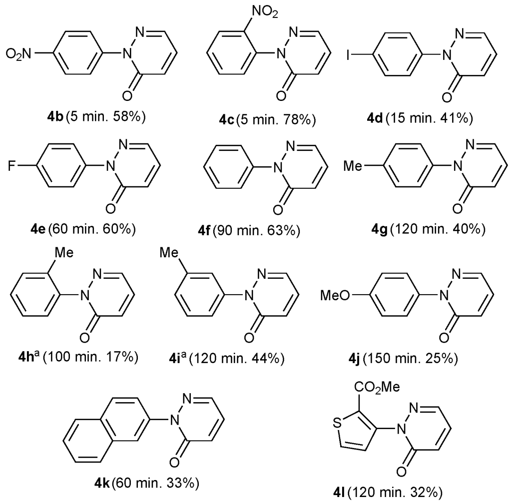
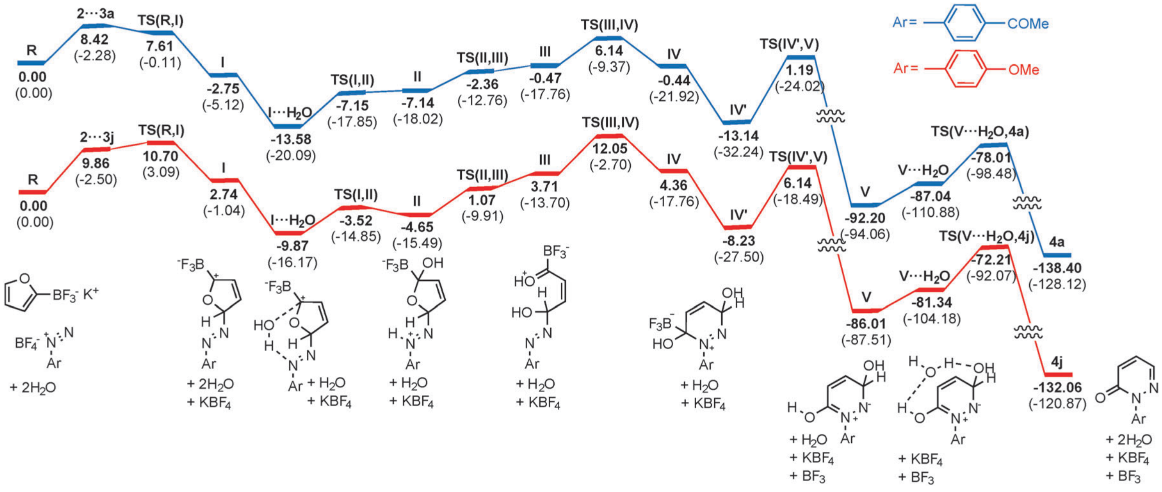


Chart 1 Synthesis of *N*-arylated pyridazinones **4**. Reaction conditions: **3** (0.42 mmol, 1 eq.) dissolved in H_2O (4 mL) was added to a stirred aqueous solution (6 mL) of **2** (0.51 mmol, 1.2 eq.) at 0–5 °C in a covered flask. Mass balance mainly corresponds to decomposition. [a] Product isolated with traces of **4**-hydrated derivative.

The next step was to study the mechanism of this process. It is well known that aryldiazonium salts have an electrophilic character in the aromatic substitution of activated rings giving the corresponding azo derivatives. Mayr *et al.*[9] have recently published that the BF_3K group in heteroayl trifluoroborates such as 2-furantrifluoroborate **2** increases the nucleophilicity of the remote position of the π-system in the electrophilic aromatic substitutions. Given this, an initial nucleophilic attack of the 5-remote position (see chart of Table 1) of the furan derivative to the nitrogen atom of the diazonium partner could be proposed. However, aryldiazonium salts have also been described as acting as dienophiles in Diels–Alder (DA) reactions with several 1,3-dienes.[10] Since the furan derivative can act as a diene, this is another possibility in our system that we wanted to consider.

To unravel the reaction mechanism for the synthesis of **4a** and **4j** we conducted DFT calculations. Geometry optimizations and frequency calculations were carried out using the Gaussian 09 program with the M06-2X/6-31G++(d,p) method under water solution simulated with the SMD method (ESI†). The Gibbs energy profiles obtained are shown in Scheme 1. We initially studied the DA cycloaddition between the aryldiazonium salt acting as a dienophile and the furan derivative as a diene but we were unable to locate the transition state (TS) and the expected product of the addition. Consequently, the DA reaction was ruled out as a possible initial step for this reaction. Fukui function calculations corroborated the result by Mayr *et al.*[9] that position 5 of the 2-furantrifluoroborate **2** is the most nucleophilic. Then, and not totally unexpectedly, the initial step is a nucleophilic attack of the 5-position of the furan derivative **2** to the terminal N atom of the diazonium partner **3** *via* **TS(R,I)** with a relatively low Gibbs energy barrier (7.6 kcal mol^{-1} for **3a** and 10.7 kcal mol^{-1} for **3j**) to afford intermediate **I**, a *trans* diazene species, in an almost thermoneutral process. The formation of a *cis* diazene species is also possible but the barriers are much higher (about 20 kcal mol^{-1}), and, therefore, these were not considered relevant species in the reaction mechanism. Not surprisingly, the barrier giving **I** is lower for the diazonium salt **3a**, as it has an electron-withdrawing substituent in the *para* position of the aryl group.[11] In support of this first step, we found that the reaction with furan instead of **2** only led to the recovery of starting materials. Furan itself is not sufficiently nucleophilic[9] to attack the aryldiazonium salt. The next step involves a nucleophilic attack of an explicit water molecule at position 2 of the furan ring and simultaneous proton transfer of a water proton to the N directly attached to the aryl ring. This process, which yields intermediate **II**, has a small Gibbs energy



Scheme 1 Gibbs energy profiles in a water solution at 298 K (electronic energies in parentheses) leading to the formation of **4a** (blue) and **4j** (red).

barrier of *ca.* 6 kcal mol^{-1}. A subsequent proton transfer of the same proton to the O of the furan ring breaks the C(5)–O bond of the five-membered ring and yields intermediate **III** in a slightly endergonic and barrierless step. The lone pair of the N bonded to the aryl ring then attacks C(2) of the initial furan ring providing the six-membered ring intermediate **IV**. **TS(III,IV)** is the stationary point with the highest energy along the reaction coordinate and the energy span between **TS(III,IV)** and intermediate **I···H$_2$O** is the energy barrier that has to be surmounted to reach the products. This energy barrier is 19.7 (Ar = *p*-C_6H_4-COMe) and 21.9 (Ar = *p*-C_6H_4-OMe) kcal mol^{-1}. The lower barrier found for **TS(IIIa,IVa)** than **TS(IIIj,IVj)** can be explained by the electron-withdrawing nature of the COMe substituent that increases the electrophilic character of the N atom. This result agrees with the experimentally observed higher reactivity of the diazonium salts containing electron-withdrawing substituents. In a subsequent step, **IV** rearranges to **IV′**, a more stable boat-shape conformational isomer. Next, **IV′** loses BF_3, which is responsible for the final acidity of the reaction medium, to form **V** with a barrier of about 14 kcal mol^{-1} in a very exergonic process. Finally, loss of a water molecule through **TS(V···H$_2$O,4)** with an energy barrier of 14.2 (Ar = *p*-C_6H_4-COMe) and 13.8 (Ar = *p*-C_6H_4-OMe) kcal mol^{-1} delivers the final product of the reaction (**4**). Therefore, it can be concluded that the O atom of the pyridazinone ring comes from a water solvent molecule.

Isotope experiments were then carried out (ESI†). The reaction between **2** and **3e** was run in D_2O and no incorporation of deuterium in the final product was detected. In the reaction run in $H_2{}^{18}O$, incorporation of ^{18}O in **4e** was detected in the final product by GC-MS in accordance with the mechanistic proposal.

We then studied the reaction that affords **4a** by electrospray ionization mass spectrometry (ESI-MS). The aqueous solution resulting from the reaction between furan **2** and **3a** was injected in ESI(−) mode. A peak at *m*/*z* = 280.9 was assigned to intermediate **I**. CID fragmentation of this compound showed the formation of a peak at [M-68]$^-$ corresponding to the loss of the BF_3 group. Another peak at *m*/*z* = 299.0 corresponded to a more advanced intermediate, probably **IV′**, supporting again the involvement of a water molecule, which after fragmentation again loses BF_3 to afford intermediate **V**. Analogous behaviour was observed for aryl diazonium salt **3e** (see ESI†).

In conclusion, a new method for the synthesis of *N*-arylated pyridazinones is described starting with potassium 2-furantrifluoroborate and several aryldiazonium tetrafluoroborates. The method is easy, fast, and simple. Furthermore, it is environmentally benign since no catalysts or additives were needed and water is used as the solvent. DFT calculations performed to elucidate the mechanism showed that the initial attack does not involve a Diels–Alder cycloaddition but rather a nucleophilic attack of the furan derivative to the diazonium partner. The reaction mechanism was corroborated by isotope labelling and ESI-MS experiments.

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