Monatshefte für Chemie - Chemical Monthly (2023) 154:1383–1390
https://doi.org/10.1007/s00706-022-02957-1

ORIGINAL PAPER

The inverse-electron demand Diels–Alder reaction of tetrazines with cyclic enol ethers

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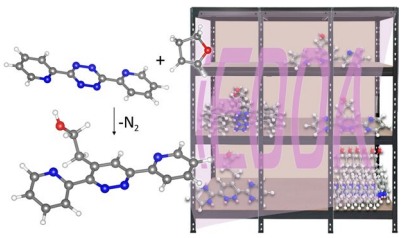
Received: 13 May 2022 / Accepted: 27 June 2022 / Published online: 26 July 2022

Abstract

Inverse electron-demand Diels–Alder additions (iEDDA) between 1,2,4,5-tetrazines and suitable unsaturated dienophiles such as olefins, alkynes, or enol ethers provide facile access to pyridazines. Herein the use of cyclic enol ether derivatives for preparing pyridazines bearing 2-hydroxyethyl, 3-hyproxypropyl, and 3-oxopropyl substituents at the 4-position is disclosed and second order rate constants for the reactions with 2,3-dihydrofuran, 3,4-dihydro-2*H*-pyran, and 2-methoxy-3,4-dihydro-2*H*-pyran are presented.

Graphical abstract



Keywords Cycloadditions · Pyridazines · Kinetics · Click-reactions

Introduction

Since the first report of the synthesis of pyridazines from tetrazines and alkenes, allenes, or alkynes by Carboni and Lindsey in 1959 [1], this reaction received ever increasing attention first because of its synthetic potential in heterocyclic chemistry [2] and later in chemical biology applications because particular tetrazine/olefin combinations provide exceptionally fast and selective ligation reactions at very low concentrations [3]. Additionally, applications in material chemistry evolved [4–6]. The mechanistic understanding of the inverse-electron demand Diels–Alder cycloaddition (iEDDA) reactions, the broader term for the reaction of a tetrazine with an olefin giving a pyridazine derivative, is well developed and nicely summarized in a recent review article [7].

A special case of dienophiles are enol ethers. Enol ethers undergo iEDDA and subsequently the primary formed dihydropyridazine product aromatizes upon fast or even spontaneous elimination of the corresponding alcohol [8–10]. This reactivity has been exploited in natural product syntheses [11, 12], but in particular in chemical biology in so-called click to release reactions [3]. A click to release reaction is a bioorthogonal bond-cleavage reaction, in this case caused by the iEDDA of tetrazine with an enol ether, releasing the corresponding alcohol. In that way, e.g., drug release can be triggered [13–15] or caged fluorophores can be unmasked and used as bioorthogonal fluorogenic probes [16].

Dedicated to the memory of Professor Fritz Sauter.

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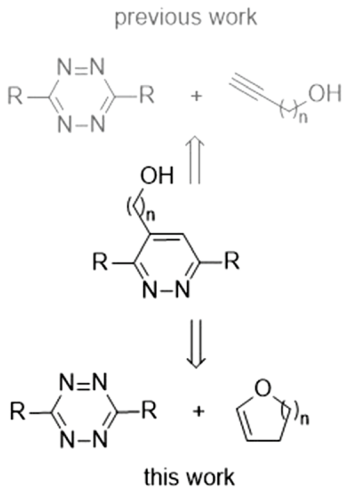
Scheme 1



Herein we wish to report the use of cyclic enol ethers as the dienophile in iEDDA reactions with tetrazines for preparing pyridazines with 2-hydroxyethyl or 3-hyproxypropyl substituents in 4-position of the pyridazine ring as an alternative for hitherto used alkynes (Scheme 1). Earlier work of Roffey and Verge [8], Sauer et al. [9], and Boger et al. [17] presented some early examples of using cyclic enol ethers. Taking into account, that many reliable and high yielding synthetic strategies for preparing many differently substituted tetrazines became available in the last years [18–20], access to many new pyridazine derivatives is facilitated by the herein disclosed methodology.

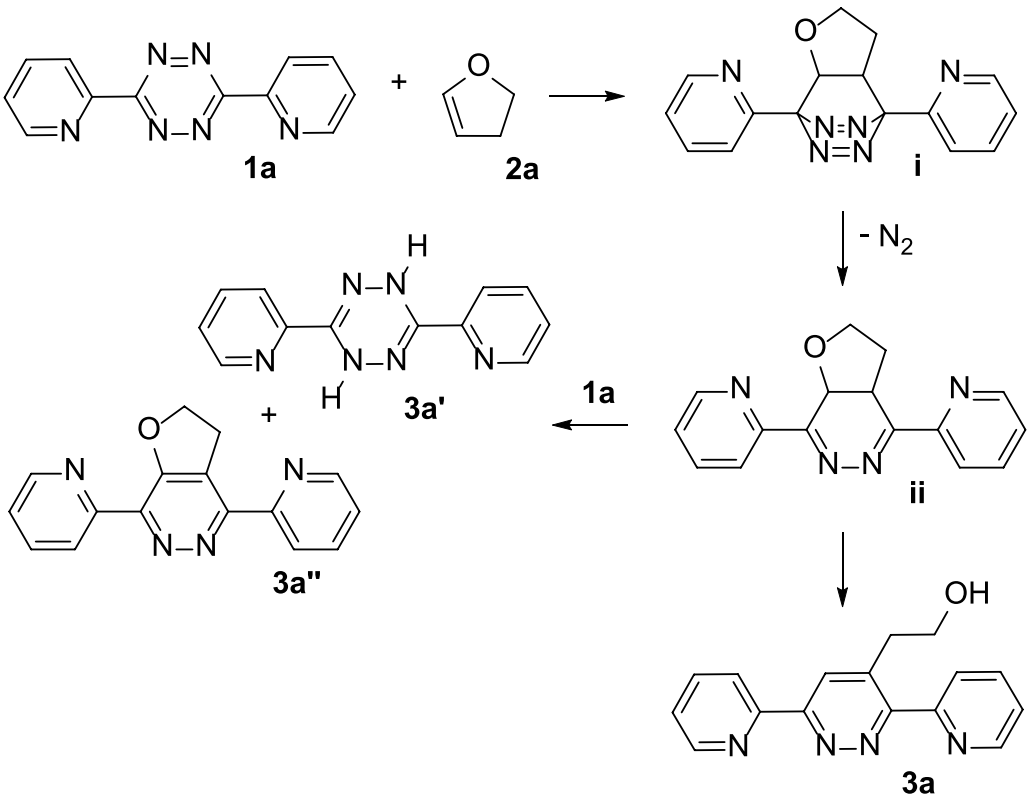
Results and discussion

As a starting point, the reaction of 3,6-di(pyridin-2-yl)-1,2,4,5-tetrazine (**1a**) with 2,3-dihydrofuran (**2a**) was investigated under different reaction conditions. Firstly, the impact of excess of olefin **2a** on the time needed for full conversion of tetrazine **1a** was studied. A fast reaction of an equimolar amount of the starting materials at room temperature is desirable for qualifying the reaction as a click reaction. However, at 23 °C in CH_2Cl_2 as the solvent the reaction is rather slow giving full conversion of **1a** in about 12 h (Table 1, entry 1). Upon increasing the excess of **2a,** the reaction becomes faster and upon using 10 equiv. of **2a**, full conversion of **1a** can be obtained after only 10 min (Table 1, entries 2–4). Increasing the temperature to 40 °C and using only a slight excess of **2a** (1.2 equiv.) gave full conversion of **1a** after 70 min (Table 1, entry 5). A further rise of the temperature to 55 °C (the boiling point of 2,3-dihydrofuran is 54–55 °C [21]) led to reaction times of 15–25 min depending on the solvent used. In less polar toluene, the reaction is distinctly slower than in dioxane or THF at the same temperature (Table 1, entries 6–8), which is in stark contrast to the iEDDA of styrenes with **1a**. In these cases, the reactions in toluene were approx. 1.5 to 2 times faster than in THF [22].Using toluene at 100 °C a similar reaction speed than obtained in THF at 55 °C can be obtained (Table 1, entry 9).

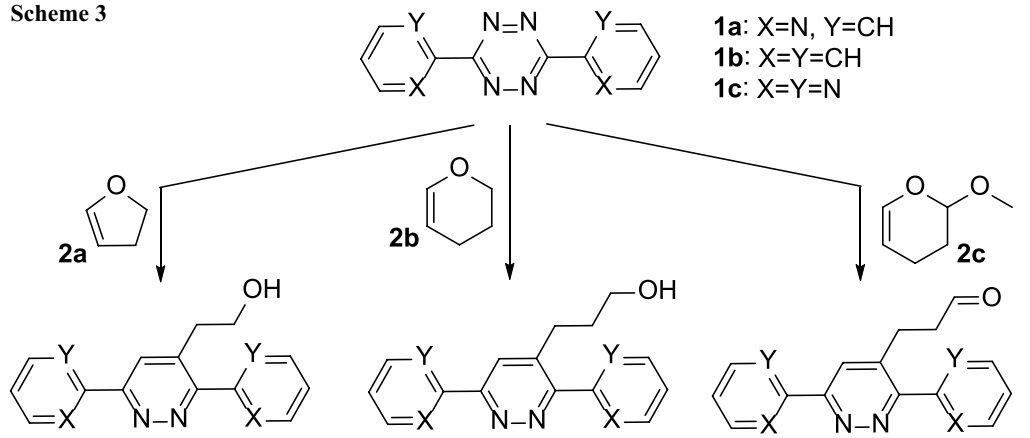
In all cases, a single main product formed, which is in every case accompanied by side products up to a share of about 10% in sum. The main product was readily identified as 4-(1-hydroxyethyl)-3,6-di(2-pyridyl)pyridazine (**3a**) upon comparison with published data [23]. The side products were found to be 3,6-di(pyridin-2-yl)-dihydrotetrazine (**3a′**) and most probably 4,7-di(pyridin-2-yl)-2,3-dihydrofuro[2,3-*d*]pyridazine (**3a″**), see Scheme 2. **3a′** and **3a″** might result from the oxidation of initially formed 2,3,3a,7-tetrahydrofuro[2,3-*d*]pyridazine intermediates by remaining **1a**. Such an oxidation of dihydropyridazine derivatives by tetrazines is known [24, 25] and would explain the similar amounts of **3a′** and **3a″** observed in the crude product mixture. Actually all attempts to suppress the formation of the side products failed (Table 1). Also running the reaction under inert atmosphere of N_2 gave similar results, so that oxidation by oxygen from air, used to oxidise dihydropyridazines [26], can be ruled out as reason for the formation of **3a″**. However, in the present case, aromatization of the pyridazine ring upon ring-opening of the 2,3-dihydrofuro moiety (i.e., elimination of the alcohol) is faster than oxidation and consequently **3a** is the by far prevailing product. Monitoring the reaction at early stages using ^{1}H NMR spectroscopy reveals the intermittent appearance of resonances tentatively assigned to 4,7-di(pyridin-2-yl)-2,3,3a,7a-tetrahydrofuro[2,3-*d*] pyridazine (**ii** in Scheme 2) the intermediate created upon extrusion of N_2 from the initially formed tetraazabarrelene derivative (denoted **i** in Scheme 2). Quantum chemical calculations on related reactions support the assignment, as the formation of the primary product **i** is found exothermic and the barrier for obtaining the distinctly more exothermic intermediate **ii** is usually rather small [27–29]. No other side products or intermediates were observed. Accordingly, the preparation of **3a** from **1a** and **2** is most economically performed with a slight excess of **2** at elevated temperature in THF (according to Table 1, entry 8). Purification was done by column chromatography and 70% yield were obtained. For comparison, the previously disclosed synthesis of **3a** starting from **1a** and 3-butyn-1-ol (2 equiv.) was performed by heating a solution in toluene at 110 °C for 75 h. In this case, **3a** was obtained in 77% yield after a purification step by column chromatography [23]. Accordingly, the use of **2a** provides a distinctly faster and resource saving access to **3a**.

In a next step, the higher homologue 3,4-dihydro-2*H*-pyran (**2b**) was used as dienophile (Scheme 3). Testing revealed a distinctly lower reactivity when compared with **2a**. At room temperature, no reasonable reactivity could be obtained and a solution of 1.2 equiv. **2b** in toluene heated

Scheme 2



Scheme 3



to 100 °C needed 16 h for full consumption of **1a**. Using 5 equiv. **2b** at otherwise same reaction conditions needed 5 h for completion. The product 4-(1-hydroxypropyl)-3,6-di(2-pyridyl)pyridazine (**3b**) was isolated in 70% yield after a column chromatographical purification step necessary for the separation of minor amounts of **3a′**. A side product similar to **3a″** was not observed.

Using 2-methoxy-3,4-dihydro-2*H*-pyran (**2c**) as the dienophile allows for the preparation of aldehyde functionalized 3-[3,6-di(pyridin-2-yl)pyridazin-4-yl]propanal (**3c**), see Scheme 3. Compound **2c** reacts even slower than **2b** and full conversion of **1a** is reached only within 48 h when using 1.2 equiv. of **2c**, toluene as the solvent and a reaction temperature of 110 °C. Compound **3c** was isolated in pure form after chromatographic work up in 54% yield.

No evidence for the likely primary product, the hemiacetal 3-[3,6-di(pyridin-2-yl)pyridazin-4-yl]-1-methoxypropan-1-ol could be retrieved.

Switching to the less electron poor and thus less reactive tetrazine derivative 3,6-diphenyl-1,2,4,5-tetrazine (**1b**) distinctly slower reactions were observed in all cases. With 1.2 equiv. **2a** full conversion of **1b** is obtained in approx. 5 d using toluene as the solvent and a reaction temperature of 100 °C. When using excess of **2a** and no further solvent, the reaction time can be shortened to about 8 h. The desired product 4-(1-hydroxyethyl)-3,6-diphenyl-pyridazine (**4a**) can be isolated upon separation of minor unidentified impurities by column chromatography in 67% yield. Similarly, 4-(1-hydroxypropyl)-3,6-diphenyl-pyridazine (**4b**) needs excess of **2b** for a reasonable short reaction time. After heating the reaction mixture for 48 h at 100 °C and similar workup as in the case of **4a**, **4b** was isolated in 53% yield. Tetrazine **1b** can also be used to prepare 3-(3,6-diphenyl) pyridazin-4-yl)propanal (**4c**). In this case, the reaction is carried out in neat **2c** for 52 h at 110 °C and after workup, 39% of the desired product is obtained.

Going for a more reactive tetrazine example, 3,6-di(pyrimidin-2-yl)-1,2,4,5-tetrazine (**1c**) was chosen. Upon reacting a dispersion of **1c** in toluene with 1.2 equiv. **2a** for 60 min at 100 °C, full conversion of the tetrazine was noted and 4-(1-hydroxyethyl)-3,6-di(pyrimidin-2-yl)-pyridazine (**5a**) was obtained in 82% yield. The relatively long reaction time is due to the poor solubility of **1c** in toluene (or in other solvents like THF or dioxane). For the reactions of **1c** with **2b** and **2c** an excess olefin and a reaction temperature of 90 °C were used. In that way, 4-(1-hydroxypropyl)-3,6-di(pyrimidin-2-yl)-pyridazine (**5b**) and 3-[3,6-di(pyrimidin-2-yl)-)pyridazin-4-yl]propanal (**5c**) were obtained, upon workup, in 54% and 72% yield, respectively. The herein presented pyridazine derivatives were characterized by ^{1}H and ^{13}C NMR spectroscopy and elemental analysis. Corresponding data do not show special features and are presented in the experimental part.

To set the reactivity of cyclic enol ethers into relation, the second order rate constants of their reactions with **1a** and **1c** were determined. For electron richer **1b**, not featuring intramolecular repulsive N–N interactions, recently identified as the decisive effect for accelerating the cycloaddition step in case of tetrazines **1a** and **1c** [30], rate constants were not determined because the reactions are very slow under the chosen measurement conditions. Results are shown in Fig. 1. The five-membered cyclic enol ether **2a** reacts approx. 200 times faster than its 6-membered homologue **2b** and about 1000 times faster than **2c**. An aspect explaining this are the different ring strains of **2a** and **2b** as it has been shown, that the reactivity of dienophiles increase with increasing ring strain [31]. A similar trend has been found when using

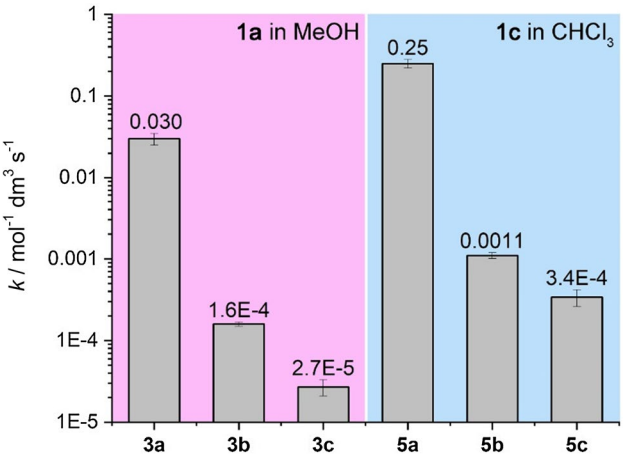


Fig. 1 Second-order rate constants for the formation of pyridazines **3a**–**3c** (determined in methanol) and **5a**–**5c** (determined in $CHCl_3$) at room temperature in a logarithmic depiction

highly reactive 1,2,4,5-tetrazine-3,6-dicarboxylate (with **2a**: $k = 437$ mol^{-1} dm^3 s^{-1}; with **2b**: $k = 1.75$ mol^{-1} dm^3 s^{-1} in 1,4-dioxane) [9].

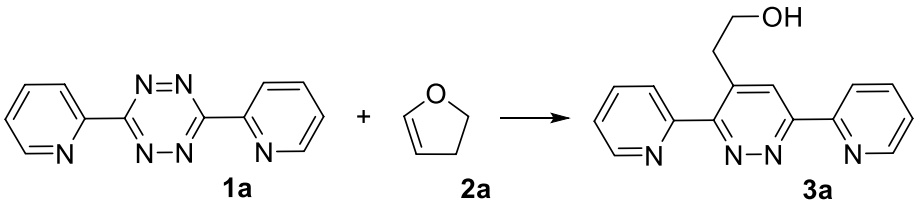
The electron poorer tetrazine **1c** reacts roughly ten times faster than **1a**, however **1a** and **1c** are investigated in different solvents. When comparing the second-order rate constants in the same solvent, a higher difference was noted as k for the reaction of **1a** with **2a** in chloroform is only 0.011 ± 0.0005 mol^{-1} dm^3 s^{-1}. The solubility of **1c** in methanol is too low to permit the rate constant determinations in this solvent.

In comparison to commonly used dienophiles, it is revealed that **2a** exhibits a second-order rate constant about an order of magnitude higher than styrene (with **1a** $k = 0.003$ mol^{-1} dm^3 s^{-1} in methanol) [32]. Cyclopentene gives a slower and norbornene a faster reaction (with **1a** $k = 0.008$ resp. 0.15 mol^{-1} dm^3 s^{-1} in methanol) than **2a** [32]. Dienophiles **2b** and **2c** can be regarded as rather slow reactants in this reaction. However, when compared to terminal alkynes, their second-order rate constants are still about an order of magnitude higher [9].

Conclusion

Using the cyclic enol ethers 2,3-dihydrofuran, 3,4-dihydro-2*H*-pyran, and 2-methoxy-3,4-dihydro-2*H*-pyran instead of the more expensive accordingly substituted alkynes provide a distinctly faster access to pyridazines bearing 2-hydroxyethyl, 3-hydroxypropyl, and 3-oxopropyl substituents at the 4-position. The five-membered ring system 2,3-dihydrofuran reacts about 200 times faster than its six-membered homologue 3,4-dihydro-2*H*-pyran and about 1000 times faster

Table 1 Time needed for full conversion of **1a** in the reaction with **2a** in dependence of different reaction conditions



Entry	**2**/equiv	Solvent	*T*/°C	*t*/min	Side product(s)/%
1	1.02	CH_2Cl_2	23	≈ 720	6
2	2	CH_2Cl_2	23	120	8
3	5	CH_2Cl_2	23	15	6
4	10	CH_2Cl_2	23	10	6
5	1.2	CH_2Cl_2	40	70	6
6	1.2	Dioxane	55	15	9
7	1.2	Toluene	55	25	10
8	1.2	THF	55	15	10
9	1.2	Toluene	100	15	10

Reaction conditions: to 50 mg **1a** dissolved in 2 cm^3 of the respective solvent the corresponding amount of **2a** was added and the reaction mixture was stirred at the given temperature in a tightly closed vessel; full conversion of **1a** was defined as the time when the initially intense purple color of the reaction mixture vanished and the reaction mixture has turned pale yellow (visual inspection). The absence of **1a** was confirmed by ^{1}H NMR spectroscopy, which in turn revealed the formation of side products, which were quantified in respect to the main product **3a**

than 2-methoxy-3,4-dihydro-2*H*-pyran. All cyclic enol ethers presented here surpass alkynes leading to the same products in their reactivity.

Experimental

Chemicals were purchased from Sigma-Aldrich, Fisher Scientific, Merck, or Alfa Aesar. All reagents were used without further purification unless otherwise noted. Tetrazines **1a**, **1b**, and **1c** were prepared according to literature [33–35]. NMR spectra were recorded on a Bruker Avance III 300 MHz FT NMR spectrometer (300.36 MHz (^{1}H), 75.53 MHz (^{13}C)). Chemical shifts δ [ppm] are referenced to residual protonated solvent signals as internal standard $CDCl_3$: $\delta = 7.26$ ppm (^{1}H), 77.16 ppm (^{13}C). Elemental analyses were conducted on an Elementar Vario Micro Cube with CHN detector at 1200 °C. Results were found to be in good agreement (±0.3%) with calculated values. Analytical thin layer chromatography (TLC) was performed on Merck silica gel 60-F_{254}, and spots were visualized by UV light or by treatment with cerium ammonium molybdate solution or potassium permanganate. Column chromatography was performed using silica gel 60 Å from Acros Organics.

The rate constants were determined under pseudo first-order conditions using UV–Vis spectroscopy. The decay in absorption of **1a** at 545 nm or of **1c** at 537 nm upon reaction with various amounts of the dienophiles **2a**–**2c** was recorded. All reactions were conducted at 23 ± 0.5 °C using methanol in case of **1a** and chloroform in case of **1c** as the solvents. Such pseudo first-order rate constants were obtained by linearly fitting the logarithmized absorption over time data and the slope of the curve fit gave the respective observed rate constants for a given dienophile concentration, which varied between 0.05 and 0.1 mol dm^{-3}. The second-order rate constants were then derived from the linear regression equitation of the observed rate constants data plotted over the concentration of the dienophiles.

2-[3,6-Di(pyridin-2-yl)pyridazin-4-yl]ethan-1-ol (3a) 500 mg **1a** (2.12 mmol, 1.0 eq) and 0.192 cm^3 **2a** (2.54 mmol, 1.2 eq) were dissolved in 10 cm^3 toluene using a tightly closed Schlenk-tube and heated at 55 °C for 15 min whereupon the colour turned to pale yellow. The solvent was removed and the remaining solid was purified by column chromatography (CH_2Cl_2/MeOH 50/1) affording 413 mg (70%) **3a** as a beige solid. NMR spectra were found to be in accordance with the ones described in Ref. [23]. R_f (CH_2Cl_2/MeOH 20/1) = 0.21; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 8.77$–8.69 (m, 2H, py^{3,6}), 8.67 (d, 1H, $^3J_{HH} = 5.0$ Hz, py^6), 8.60 (s, 1H, pz^5), 8.30 (d, 1H, $^3J_{HH} = 8.0$ Hz, py^3), 7.97

(m, 1H, py^4), 7.89 (m, 1H, py^4), 7.46 (m, 1H, py^5), 7.40 (m, 1H, py^5), 6.7 (bs, 1H, –OH), 4.15 (t, 2H, CH_2CH_2OH), 3.16 (t, 2H, CH_2CH_2OH) ppm; $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, 25 °C): $\delta = 159.0$, 157.3, 155.0, 153.4 (4C, q, py^2, $pz^{3,6}$), 149.6, 147.5 (2C, py^6), 140.6 (1C, q, pz^4), 138.2, 137.3 (2C, py^4), 126.7, 125.9, 124.9, 124.2, 122.0 (5C, $py^{3,5}$, pz^5), 63.6 (1C, CH_2CH_2OH), 34.7 (1C, CH_2CH_2OH) ppm.

4,7-Di(pyridin-2-yl)-2,3-dihydrofuro[2,3-*d*]pyridazine (3a″, $C_{16}H_{12}N_4O$) 3a″ was isolated from the same column chromatography performed for the isolation of **3a** giving 18 mg (3%) of **3a″**. R_f (CH_2Cl_2/MeOH 20/1) = 0.34; ^1H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 8.84$ (m, 1H, py^6), 8.78–8.69 (m, 2H, $py^{3,6}$), 8.51 (d, 1H, $^3J_{HH} = 7.9$ Hz, py^3), 7.90 (dt, 2H, $^3J_{HH} = 7.8$ Hz, $^4J_{HH} = 1.5$ Hz, py^4), 7.37 (m, 2H, py^5), 4.93 (t, 2H, CH_2CH_2O), 3.90 (t, 2H, CH_2CH_2O) ppm; $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, 25 °C): $\delta = 160.3$ (1C, q, pz^8), 155.12, 155.07, 154.1 (3C, q, py^2, pz^4), 149.5, 149.1 (2C, py^6), 145.0 (1C, q, pz^7), 136.94, 136.87 (2C, py^4), 128.2 (1C, q, pz^3), 124.1, 123.9, 123.4, 122.9 (4C, $py^{3,5}$), 73.5 (1C, CH_2CH_2O), 30.0 (1C, CH_2CH_2O) ppm.

3-[3,6-Di(pyridine-2-yl)pyridazine-4-yl]propan-1-ol (3b) In a tightly closed Schlenk-tube a solution of 500 mg **1a** (2.12 mmol, 1.0 eq) and 0.230 cm^3 **2b** (2.54 mmol, 1.2 eq) in 10 cm^3 toluene was heated at 100 °C for 16 h. The solvent was removed and the remaining solid was purified by column chromatography (CH_2Cl_2/MeOH 50/1) affording 430 mg (70%) **3b**. NMR spectra were found to be in accordance with the ones described in Ref. [23]. R_f (CH_2Cl_2/MeOH 10/1) = 0.71; ^1H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 8.78$–8.69 (m, 2H, $py^{3,6}$), 8.67 (d, 1H, $^3J_{HH} = 4.8$ Hz, py^6), 8.56 (s, 1H, pz^5), 8.18 (d, 1H, $^3J_{HH} = 8.1$ Hz, py^3), 7.93 (m, 2H, py^4), 7.42 (m, 2H, py^5), 5.3 (s, $CH_2CH_2CH_2OH$), 3.60 (m, 2H, $CH_2CH_2CH_2OH$), 3.12 (t, 2H, $CH_2CH_2CH_2OH$), 2.13 (qt, 2H, $CH_2CH_2CH_2OH$) ppm; $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, 25 °C): $\delta = 159.1$, 157.4, 155.8, 153.4 (4C, q, py^2, $pz^{3,6}$), 149.6, 147.9 (2C, py^6), 141.7 (1C, q, pz^4), 137.9, 137.4 (2C, py^4), 126.2, 125.9, 124.9, 124.1, 122.0 (5C, $py^{3,5}$, pz^5), 60.0 (1C, $CH_2CH_2CH_2OH$), 33.1 (1C, $CH_2CH_2CH_2OH$), 27.2 (1C, $CH_2CH_2CH_2OH$) ppm.

3-[3,6-Di(pyridine-2-yl)pyridazine-4-yl]propanal (3c, $C_{17}H_{14}N_4O$) 500 mg **1a** (2.12 mmol, 1.0 eq) and 290 mg **2c** (2.54 mmol, 1.2 eq) were dissolved in 10 cm^3 toluene and heated to 110 °C for 2 days. Purification was achieved by column chromatography (cyclohexane/ethyl acetate 5/1) releasing 328 mg (54%) of **3c**. R_f (cyclohexane/ethyl acetate 5/1) = 0.48; ^1H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 9.80$ (s, 1H, CHO), 8.74–8.61 (m, 3H, $py^{3,6}$), 8.50 (s, 1H, pz^5), 8.23 (d, 1H, $^3J_{HH} = 7.6$ Hz, py^3), 7.86 (m, 2H, py^4), 7.35 (m, 2H, py^5), 3.37 (m, 2H, CH_2CH_2COH), 2.98 (t, 2H, CH_2CH_2COH) ppm; $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, 25 °C): $\delta = 200.0$ (C, CH_2CH_2CHO), 158.2, 156.9, 155.5, 152.8 (4C, q, py^2, $pz^{3,6}$), 149.1, 148.2 (2C, py^6), 140.5 (1C, q, pz^4), 136.8, 136.6 (2C, py^4), 125.7, 124.4, 124.3, 123.4, 121.3 (5C, $py^{3,5}$, pz^5), 43.7 (1C, CH_2CH_2CHO), 25.3 (1C, CH_2CH_2CHO) ppm.

2-(3,6-Diphenylpyridazin-4-yl)ethan-1-ol (4a, $C_{18}H_{16}N_2O$) 500 mg **1b** (2.15 mmol, 1.0 eq) and 1 cm^3 **2a** (excess) were placed in a tightly closed Schlenk tube and heated to 100 °C for 8 h. Purification was achieved by column chromatography (cyclohexane/ethyl acetate 5/1 changing to cyclohexane/ethyl acetate 1/1) giving 395 mg (66%) of **3c**. R_f (cyclohexane/ethyl acetate 10/1) = 0.20; ^1H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 8.02$–7.93 (m, 2H, $ph^{2,6}$), 7.81 (s, 1H, pz^5), 7.49–7.42 (m, 2H, $ph^{2,6}$), 7.36 (m, 6H, $ph^{3,4,5}$), 4.14 (bs, 1H, CH_2CH_2OH), 3.65 (t, 2H, CH_2CH_2OH), 2.81 (t, 2H, CH_2CH_2OH) ppm; $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, 25 °C): $\delta = 160.8$, 157.3 (2C, q, $pz^{3,6}$), 137.8, 136.9, 136.2 (3C, q, pz^4, ph^1), 129.6, 129.1, 128.7, 128.5, 128.2, 126.9 (10C, $ph^{2,3,4,5,6}$), 125.0 (1C, pz^5), 60.5 (CH_2CH_2OH), 34.7 (1C, CH_2CH_2OH) ppm.

3-(3,6-Diphenylpyridazin-4-yl)propan-1-ol (4b, $C_{19}H_{18}N_2O$) 50 mg **1b** (0.215 mmol, 1.0 eq) was dissolved in 1 cm^3 **2b** and heated to 100 °C for 48 h. Column chromatography (cyclohexane/ethyl acetate 5/1 changing to cyclohexane/ethyl acetate 1/1) released 33 mg (53%) of **4b**. R_f (cyclohexane/ethyl acetate 10/1) = 0.22; ^1H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 8.14$ (m, 2H, $ph^{2,6}$), 7.78 (s, 1H, pz^5), 7.65–7.58 (m, 2H, $ph^{2,6}$), 7.58–7.44 (m, 6H, $ph^{3,4,5}$), 3.59 (t, 2H, $CH_2CH_2CH_2OH$), 2.86 (t, 2H, $CH_2CH_2CH_2OH$), 1.81 (m, 2H, $CH_2CH_2CH_2OH$) ppm; $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, 25 °C): $\delta = 160.9$, 157.9 (q, 2C, $pz^{3,6}$), 140.2, 137.2, 136.5 (q, 3C, pz^4, ph^1), 130.0, 129.3, 129.1, 129.0, 128.6, 127.2 (10C, $ph^{2,3,4,5,6}$), 124.4 (1C, pz^5), 61.7 (1C, $CH_2CH_2CH_2OH$), 32.4 (1C, $CH_2CH_2CH_2OH$), 28.6 (1C, $CH_2CH_2CH_2OH$) ppm.

3-(3,6-Diphenylpyridazin-4-yl)propanal (4c, $C_{19}H_{16}N_2O$) 50 mg **1b** (0.215 mmol, 1.0 eq) was dissolved in 1 cm^3 **2c** and heated to 110 °C for 52 h. Column chromatography (cyclohexane/ethyl acetate 5/1 changing to cyclohexane/ethyl acetate 1/1) gave 24 mg (39%) of **4c**. R_f (cyclohexane/ethyl acetate 1/1) = 0.57; ^1H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 9.70$ (s, 1H, CH_2CH_2CHO), 8.12 (m, 2H, $ph^{2,6}$), 7.8 (s, 1H, pz^5), 7.63–7.45 (m, 8H, $ph^{2,3,4,5}$), 3.10 (t, 2H, CH_2CH_2CHO), 2.69 (t, 2H, CH_2CH_2CHO) ppm; $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, 25 °C): $\delta = 199.6$ (1C, CH_2CH_2CHO), 160.6, 158.0 (q, 2C, $pz^{3,6}$), 138.7, 137.0, 136.3 (q, 3C, pz^4, ph^1), 130.1, 129.2, 129.1, 128.8, 127.2 (10C, $ph^{2,3,4,5,6}$), 124.4 (1C, pz^4), 43.0 (1C, CH_2CH_2CHO), 24.7 (1C, CH_2CH_2CHO) ppm.

2-[3,6-Di(pyrimidin-2-yl)pyridazin-4-yl]ethan-1-ol (5a, $C_{14}H_{12}N_6O$) 110 mg **1c** (0.462 mmol, 1.0 eq) and 0.042 cm^3 **2a** (0.455 mmol, 1.2 eq) were dispersed in 1 cm^3 toluene and heated at 100 °C for 60 min. Flash chromatography (CH_2Cl_2/MeOH 10:1) yielded 106 mg (82%) of **5a**. R_f (CH_2Cl_2/MeOH 10/1) = 0.24; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 8.95 (d, 4H, $^3J_{HH}$ = 4.7 Hz, $pr^{4,6}$), 8.62 (s, 1H, pz^5), 7.45 (t, 1H, $^3J_{HH}$ = 4.7 Hz, pr^5), 7.39 (t, 1H, $^3J_{HH}$ = 4.9 Hz, pr^5), 4.04 (t, 3H, CH_2CH_2OH), 3.08 (t, 2H, CH_2CH_2OH) ppm; ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$, 25 °C): δ = 163.3, 161.9 (2C, q, pr^2), 159.0, 157.0 (2C, q, $pz^{3,6}$), 157.9, 157.5 (4C, $pr^{4,6}$), 139.8 (1C, q, pz^4), 128.6 (1C, pz^5), 121.3, 120.8 (2C, pr^5), 62.7 (1C, CH_2CH_2OH), 34.7 (1C, CH_2CH_2OH) ppm.

3-[3,6-Di(pyrimidin-2-yl)pyridazin-4-yl]propan-1-ol (5b, $C_{15}H_{14}N_6O$) 100 mg **1c** (0.426 mmol, 1.0 eq) was dispersed in 1 cm^3 3,4-dihydro-2*H*-pyran and stirred at 90 °C for 40 min. The crude product was purified using column chromatography (CH_2Cl_2/MeOH 20/1) giving 67 mg (53%) of **5b**. R_f (CH_2Cl_2/MeOH 10/1) = 0.25; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 8.97 (m, 4H, $pr^{4,6}$), 8.58 (s, 1H, pz^5), 7.45 (t, 1H, $^3J_{HH}$ = 4.9 Hz, pr^5), 7.41 (t, 1H, $^3J_{HH}$ = 4.9 Hz, pr^5), 3.59 (t, 2H, $CH_2CH_2CH_2OH$), 3.5 (bs, 1H, $CH_2CH_2CH_2OH$), 2.98 (t, 2H, $CH_2CH_2CH_2OH$), 2.00 (m, 2H, $CH_2CH_2CH_2OH$) ppm; ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$, 25 °C): δ = 163.9, 162.0 (q, 2C, pr^2), 159.1, 157.0 (q, 2C, $pz^{3,6}$), 158.0, 157.5 (4C, $pr^{4,6}$), 141.4 (q, 1C, pz^4), 127.8 (1C, pz^5), 121.3, 120.8 (2C, pr^5), 60,8 (1C, $CH_2CH_2CH_2OH$), 32.6 (1C, $CH_2CH_2CH_2OH$), 27.6 (1C, $CH_2CH_2CH_2OH$) ppm.

3-[3,6-Di(pyrimidin-2-yl)pyridazin-4-yl]propanal (5c, $C_{15}H_{12}N_6O$) 51 mg **1c** (0.213 mmol, 1.0 eq) was dispersed in 1 cm^3 **2c** and stirred at 90 °C for 80 min. The crude product was purified via column chromatography (CH_2Cl_2/MeOH 20:1) giving 45 mg (72%) **5c**. R_f (CH_2Cl_2/MeOH 10/1) = 0.36; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 9.81 (s, 1H, CH_2CH_2CHO), 8.99 (m, 4H, $pr^{4,6}$), 8.58 (s, 1H, pz^5), 7.44 (m, 2H, pr^3), 3.22 (t, 2H, CH_2CH_2CHO), 2.96 (t, 2H, CH_2CH_2CHO) ppm; ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$, 25 °C): δ = 199.9 (1C, CH_2CH_2CHO), 163.9 (q, 2C, pr^2), 158.0, 157.6 (4C, $pr^{4,6}$), 157.1 (q, 2C, $pz^{3,6}$), 140.5 (q, 1C, pz^4), 128.0 (1C, pz^5), 121.4, 120.8 (2C, pr^5), 44.0 (1C, CH_2CH_2CHO), 24.9 (1C, CH_2CH_2CHO) ppm.

Acknowledgements ACK acknowledges the Austrian Science Fund for receiving a Lise Meitner fellowship [T 578-N19].

Funding Open access funding provided by Graz University of Technology.

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