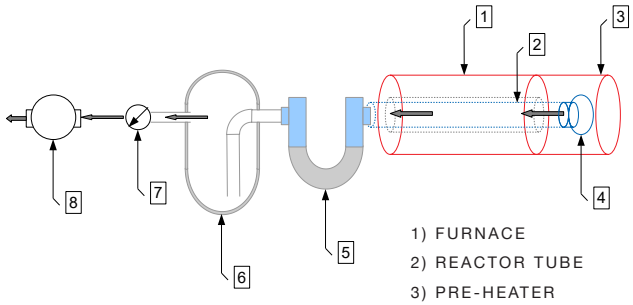
FLASH PYROLYSIS PLATFORM

Flash vacuum pyrolysis, the key step in the synthesis of a novel oxadiazolo-pyrimidinone library



1) FURNACE
2) REACTOR TUBE
3) PRE-HEATER
4) SAMPLE VIAL
5) COLD TRAP 1.
6) COLD TRAP 2.
7) 3-WAY VACUUM TAP ROUTER
8) VACUUM PUMP

Introduction

The synthesis of previously unexplored ring systems is of particularly high interest, especially in the pharmaceutical industry. Yet, it has been shown that medicinal chemists employ a relatively small chemical technology toolbox,1 and only a minor part of the synthetically tractable small aromatic systems can be found in the literature.[2]

STATE OF THE ART: Thermal cyclizations in batch are normally performed in solvents with high boiling points (e.g. diphenyl ether, b.p. 258°C). However, such processes are often hampered by side-reactions and by difficult work-up.[5,6] Beneficially, high temperature / high pressure flow chemistry (e.g. in the Phoenix Flow Reactor) allows to apply low boiling point solvents (e.g. CH_3CN, THF) in combination with the precise control of residence time.[6]

Although flash vacuum pyrolysis is not a generally accepted method in pharmaceutical R&D, it is often advantageous when other methods afford low selectivity or the synthesis is problematic (e.g. due to clogging) in micro- or mesofluidic flow reactors.[3]

In this application note we show how the flash vacuum pyrolysis technique is used as a key step in the synthesis of a novel oxadiazolo-pyrimidinone library.[3,4]

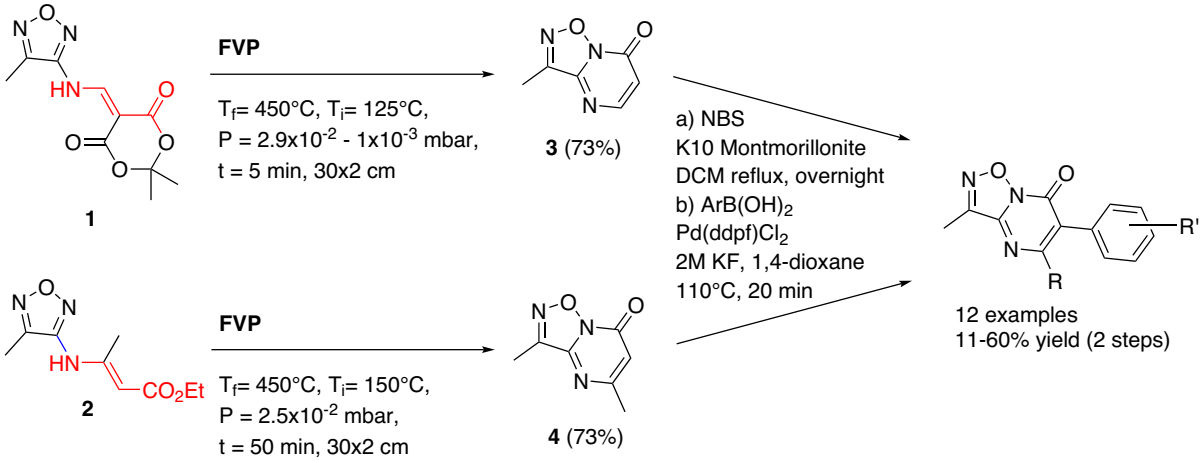
Instrumentation

Flash vacuum pyrolysis (FVP) experiments are carried out by sublimation or distillation of a substrate in vacuum through a heated reactor tube (typically quartz). The product is collected after the reactor tube in a cooled trap (dry ice / acetone or liquid nitrogen).

FVP is well suited for monomolecular transformations. Due to the low pressure (vacuum) the number of collisions between the molecules is low. Moreover, the vacuum increases the speed of migration of particles through the reactor zone resulting in short residence times (typically in the millisecond range). These properties collectively minimalize the chance for side-product formation.

Experimental

FVP experiments were carried out in the Flash Reactor Plus™ system by sublimation or distillation of the substrate in vacuum through a heated quartz reactor tube. Products were trapped in a U-tube situated at the exit point of the furnace and cooled with dry ice/acetone. Pyrolysis conditions are quoted as follows: substrate, quantity, furnace temperature (T_f), inlet temperature (T_i), pressure (range if appropriate) (P), pyrolysis time (t), tube



dimensions (length × inner diameter). The pyrolysis time is defined as the time needed for the distillation (sublimation) of the substrate through the hot tube.

RISK ASSESSMENT AND HAZARDS. The same safety precautions must be taken as for vacuum distillation. The glass components should be carefully examined for scratches and cracks which present the risk of implosions when the vacuum is applied. Appropriate personal protective equipment must be worn.

THE SYNTHESIS OF 1 AND 2

2,2-Dimethyl-5-{[(4-methyl-1,2,5-oxadiazol-3-yl)amino]methylidene}-1,3-dioxane-4,6-dione (1). Meldrum's acid (680 mg, 4.72 mmol) and triethyl orthoformate (4.7 mL, 28.26 mmol) were combined in a 25 mL round bottom flask equipped with a reflux condenser. The mixture was stirred and heated at 145°C for 2 h. The dark yellow solution was cooled to room temperature, and 4-methyl-1,2,5-oxadiazole-3-amine (430 mg, 4.34 mmol) was added. The mixture was stirred at room temperature for 1.5 h, and then the solution was concentrated under vacuum. The crude product was washed with water and cold ethanol. The white crystals were dried under vacuum over P_2O_5. Yield: 700 mg (2.76 mmol, 64%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.07 (s, 1H), 8.41 (s, 1H), 2.42 (s, 3H), 1.70 (s, 3H). ^{13}C{1H} NMR (101 MHz, DMSO): δ 163.4, 162.3, 155.3, 153.4, 147.2, 105.1, 90.6, 26.8, 7.8. HRMS ESI calcd for $C_7H_6N_3O_4$, 196.0358 $[M-C_3H_6O+H]^+$; found, 196.0356 $[M-C_3H_6O+H]^+$.

Ethyl 3-((4-methyl-1,2,5-oxadiazol-3-yl)amino)but-2-enoate (2). 4-methyl-1,2,5-oxadiazol-3-amine (500 mg, 5.05 mmol), ethyl 3-oxobutanoate (808 µL, 6.41 mmol) and catalytic amount of PTSA (17 mg. 0.1 mmol) were combined in a 25 mL round bottom flask equipped with a Dean-Stark distillation trap. The mixture was stirred in refluxing toluene (14 mL) overnight. The mixture was cooled and concentrated under vacuum. The residue was purified by column chromatography (silica, heptane/EtOAc 1:1) to yield the product as a white solid (498 mg, 2.36 mmol, 47%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.96 (s, 1H), 5.0 (s, 1H), 4.18 (q, J = 7.1 Hz, 2H), 2.40 (s, 3H), 2.39 (s, 3H), 1.30 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6): δ 169.8, 156.6, 152.1, 146.8, 92.6, 59.8, 21.5, 14.7, 7.5. HRMS ESI calcd for $C_9H_{14}N_3O_3$, 212.1035 $[M+H]^+$; found, 212.1032 $[M+H]^+$.

FVP EXPERIMENTS, THE SYNTHESIS OF 3 AND 4

3-Methyl-7H-[1,2,5]oxadiazolo[2,3a]pyrimidin-7-one (3). FVP of 1 (220 mg, 0.869 mmol, T_f = 450°C, T_i = 125°C, P = 2.9x10^{-2} - 1x10^{-3} mbar, t = 5 min, 30x2 cm) gave 3 as a white sticky solid. The product was purified by column chromatography (silica, hexane - diethyl ether) to give a white crystalline solid (96 mg, 0.635 mmol, 73% yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 (d, J = 6.5 Hz, 1H), 6.59 (d, J = 6.5 Hz, 1H), 2.53 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6): δ 155.6, 152.7, 152.3, 147.2, 110.2, 8.6. ^{15}N NMR (extracted from ^{1}H/^{15}N HMBC, DMSO-d_6): δ 377, 263, 226. HRMS ESI calcd for $C_6H_6N_3O_2$, 152.0460 $[M+H]^+$; found, 152.0481 $[M+H]^+$.

3,5-dimethyl-7H-[1,2,5]oxadiazolo[2,3-a]pyrimidin-7-one (4). FVP of 2 (1.27 g, 6.01 mmol, T_f = 450°C, T_i = 150°C, P = 2.5x10^{-2} mbar, t = 50 min, 30×2 cm) gave 4 as a white solid. The product was scraped out from the tube and purified by column chromatography (silica, hexane : ethyl acetate = 3:2) to give 4 as a white solid (726 mg, 4.51 mmol, 73% yield). 1H NMR (300 MHz, $CDCl_3$): δ 6.34 (s, 1H), 2.59 (s, 3H), 2.47 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6): δ 166.4, 152.4, 152.1, 146.2, 107.9, 23.3, 8.7. HRMS ESI calcd for $C_7H_7N_3O_2$, 166.0617 $[M+H]^+$; found, 166.0612 $[M+H]^+$.

Results and discussion

The synthesis of **3** was carried out by vacuum distillation of substrate **1** through the heated quartz reactor tube (450°C furnace temperature, 30×2 cm tube dimensions) of the FVP unit of the Flash Reactor Plus™. The ring-closed product (**3**) was collected after the reactor tube in a cooled trap at -78°C (dry ice/acetone). The structural confirmation of compound **3** was established by detailed NMR spectroscopic analysis (^{1}H, ^{13}C{^{1}H }, ^{1}H-^{15}N HMBC, ^{1}H-^{13}C HSQC, ^{1}H-^{13}C HSQMBC), and its elemental composition was confirmed by HRMS spectrometric analysis. All analytical data was in correspondence with the proposed structure. Synthesis and characterisation of compound **4** was done analogously. Next, compounds **3** and **4** were treated with *N*-bromosuccinimide under standard batch conditions to afford the brominated products (not shown on the scheme). Subsequent Suzuki-coupling with aryl boronic acids afforded **5**.

Conclusion

We demonstrated how the flash vacuum pyrolysis technique can afford previously non-described heterocycles. These heterocycles were then derivatized to afford a library of more than 20 oxadiazolo-pyrimidinones.[3,4]

Acknowledgement

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