THALESNano

PHOENIX

Safe and efficient Diels-Alder cycloaddition reactions under continuous flow

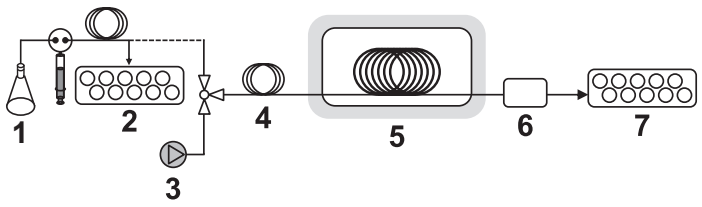


Figure 1. Schematic view of the applied instrument[3,4]

1. Solvent reservoir; 2. Autosampler; 3. HPLC pump; 4. Injection loop; 5. Phoenix Flow Reactor™; 6. Back pressure regulator; 7. Fraction collector.

Introduction

Modern flow chemistry methods offer new chemical space for drug discovery programs: novel compounds can be synthesized in dedicated high temperature/high pressure (high T/p) reactors, while reaction times can be shortened dramatically.[1,2]

State of the art: Thermal electrocyclic ring-opening reactions traditionally require high temperatures and prolonged heating.[3] Due to effective heat transfer and precise control of the parameters, the application of high T/p continuous flow technology enables these reactions to proceed with significantly shorter reaction times compared to batch or microwave methods. Tsoung and coworkers described a new approach for Gould-Jacobs reactions in their publication, which exploits the advantages of the Phoenix Flow Reactor™, as the part of an in-house modified automated system.[4]

In this application note, we present their new achievements with this instrument: first, highly reactive dienes (*ortho*-quinodimethanes) were *in situ* generated by thermal electrocyclic ring-opening of benzocyclobutanes and related cyclic moieties, then benzoisoindoles, benzocyclobutanes and other triple-annulated, biologically active heterocyclic fragments were synthesized in Diels-Alder cycloaddition (DA) reactions, applying high T/p continuous flow technology within short residence times (< 4 minutes, **Scheme 1.**).[5]

Instrumentation

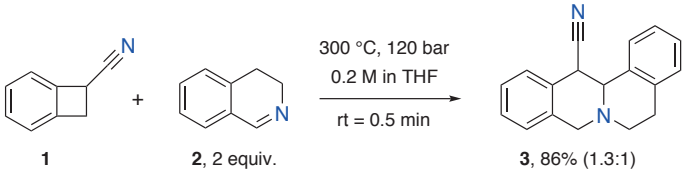
Phoenix Flow Reactor™ is designed to perform reactions up to 450 °C. The pressure range can exceed up to 200 bar applying a back pressure regulator.

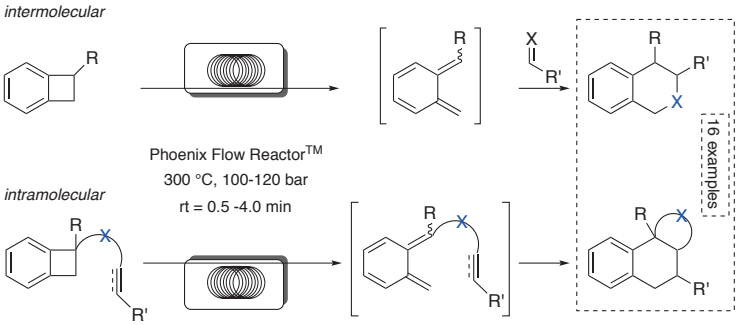
The Phoenix Flow Reactor™ (5, with a 2 mL stainless steel coil reactor) was supplemented with the following (**Figure 1.**): a solvent reservoir (1), an automated sample processor (2), an HPLC pump (3, to ensure the continuous flow of the reagents), a 10-port injector valve with a pair of 5 mL stainless steel loops (4), a back pressure regulator (6, for keeping the organic solvents in liquid phase even above their boiling points) and a fraction collector (7).

Risk assessment and hazards: Always use the system in a well ventilated fume hood to avoid inhalation of solvent vapors. Never open it at high pressure or temperature, the overheated or pressurized solvents can cause injuries. Avoid contact with the heated parts.

Experimental

*The synthesis of **3** (intermolecular DA):*



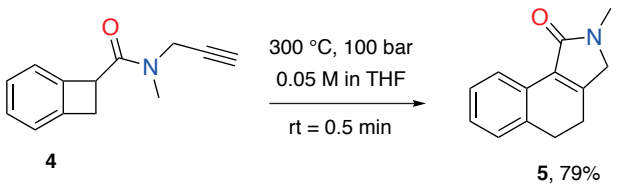


Scheme 1. Inter- and intramolecular Diels-Alder cycloaddition reactions of *ortho*-quinodimethanes

13a-phenyl-6,8,13,13a-tetrahydro-5H-isoquinolino[3,2-a]isoquinoline-13-carbonitrile (3): 1-benzocyclobutane-carbonitrile (**1**, 19.0 mg, 0.15 mmol) and 3,4-dihydroisoquinoline (**2**, 2.0 equiv., 39 mg, 0.30 mmol) were dissolved in 750 µL tetrahydrofuran (THF). The Phoenix Flow Reactor™ was set to 120 bar pressure, 300 °C temperature and 4.0 mLmin^{-1} flow rate. After the system reached the stable state, the mixture was injected to the reactor. The crude reaction mixture was collected, concentrated and purified by column chromatography. Product **3** was formed in a 1.3:1 *cis/trans* ratio, confirmed by ^{1}H NMR analysis, in 85% yield (33 mg, 0.13 mmol). Crystallization from dichloromethane/diethyl ether afforded the *cis* product.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 – 7.15 (m, 8H), 4.37 (d, J = 3.2 Hz, 1H), 4.17 (d, J = 15.2 Hz, 1H), 4.03 – 3.92 (m, 1H), 3.79 (d, J = 15.2 Hz, 1H), 3.32 (ddd, J = 17.3, 12.2, 5.2 Hz, 1H), 3.22 (ddd, J = 10.9, 5.2, 2.4 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 136.1, 134.8, 133.4, 129.3, 129.3, 128.4, 128.4, 127.2, 127.1, 126.8, 126.6, 125.3, 119.1, 61.3, 57.7, 50.3, 39.3, 29.3. HRMS (ESI/TOF-Q) m/z: $[M+H]^+$ calcd for $C_{18}H_{17}N_2$: 261.1386; found: 261.1393.

*The synthesis of **5** (intramolecular DA):*



4 **5**, 79%

2-methyl-2,3,4,5-tetrahydro-1H-benzo[e]isoindol-1-one (5): *N*-methyl-*N*-(prop-2-yn-1-yl)bicyclo[4.2.0]octa-1,3,5-triene-7-carboxamide (**4**) (30 mg, 0.15 mmol) was dissolved in 3.0 mL of THF. Subsequently, 100 bar, 300 °C and 4.0 mLmin^{-1} flow rate was set on the Phoenix Flow Reactor™. After the system reached the stable state, the mixture was injected to the 2 mL stainless steel reactor. The crude reaction mixture was collected, concentrated and purified by preparative HPLC (15-45% NH_4OAc/ACN method) to afford the product in 79% yield (24 mg, 0.12 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (d, J = 7.8 Hz, 1H), 7.30 – 7.13 (m, 3H), 3.97 (s, 2H), 3.11 (s, 3H), 2.98 (t, J = 8.2 Hz, 2H), 2.61 (t, J = 8.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.9, 149.9, 134.4, 129.2, 129.2, 127.7, 127.5, 126.9, 123.6, 54.0, 29.0, 27.9, 22.9. HRMS (ESI/TOF-Q) m/z: $[M+Na]^+$ calcd for $C_{13}H_{13}NNaO$: 222.0889; found: 222.0896.

Results and discussion

The *intermolecular Diels-Alder cycloaddition* of different imine dienophiles to 1-benzocyclobutane-carbonitrile (**1**) was investigated in the Phoenix Flow Reactor™ at 300 °C and 120 bar. The reactions were regiospecific (*cis/trans* ratios were determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture) and complete conversion was achievable in just 30 seconds in all cases. (In comparison, the batch and microwave processes required 6 hours (7% conversion) and 1 hour (complete conversion) at 180 °C, respectively). In the tested *intramolecular reactions* olefins and acetylenes gave only the *cis*-products in good yields (79% for product **5**). Reactions with siloxy compounds were also tested, affording alkyl silyl ether and vinyl silyl ether. Aldehydes and nitriles also participated in the Diels-Alder reaction in moderate yields. In case of 1,2-disubstituted alkenes, the formation of both diastereomers of the product were observed. To avoid the dimerization of the starting compounds in the synthesis of benzoisoindoline-like products more dilute (0.05 M) conditions were needed.

Dihydrobenzothiophene-2,2-dioxides and benzoisothiazoline-2,2-dioxides can also serve as precursors of *ortho*-quinodimethanes which can be generated via thermal cheletropic extrusion of SO_2. They were also tested in the intramolecular Diels-Alder reactions with olefins and acetylenes: the expected products were obtained in good yields but the reactions required longer residence times (4 minutes).

Conclusion

Through the selected examples from the research of Tsoung and coworkers, we demonstrated the advantages of the Phoenix Flow Reactor™ in various Diels-Alder cycloaddition reactions. The synthesis of different biologically active fused heterocyclic compounds was achieved by the electrocyclic ring opening reactions of benzocyclobutanes, benzothiophene-2,2-dioxides and benzoisothiazoline-2,2-dioxides and the subsequent DA reactions with several dienophiles. The application of high T/p flow methodology allowed full conversion in less than 4 minutes in a safe and reliable process.

Acknowledgement

ThalesNano would like to thank the authors for their contribution.

REFERENCES

1) Darvas, F.; Hessel, V.; Dormán, Gy. (Eds.); *Flow Chemistry Volume 1: Fundamentals*, **2014**, Berlin/Boston, De Gruyter 2) Sipos, G.; Gyollai, V.; Sipőcz, T.; Dormán, Gy.; Kocsis, L.; Jones, R.V.; Darvas, F.; *J. Flow Chem.* **2013**, *3,* 51–58. 3) Kametani, T.; Yukawa, H.; Suzuki, Y.; Honda, T.; *J. Chem. Soc., Perkin Trans. 1* **1985**, 2151–2154. 4) Tsoung, J.; Bogdan, A. R.; Kantor, S.; Wang, Y.; Charaschanya, M.; Djuric, S. W.; *J. Org. Chem.* **2017**, *82*, 1073–1084. 5) Tsoung, J.; Wang, Y.,; Djuric, S. W.; *React. Chem. Eng.* **2017**, *2,* 458–461.

ThalesNano Inc.
Zahony u. 7., H-1031 Budapest, Hungary
Tel.: +36 1 880 8500 Fax: +36 1 880 8501
E-mail: sales@thalesnano.com