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► **To cite this version:**

Maria Ivanova, Thomas Poisson, Philippe Jubault, Julien Legros. Flow platform for the synthesis of benzodiazepines. *Journal of flow chemistry*, In press, 10.1007/s41981-022-00243-z . hal-03838947

**HAL Id: hal-03838947**

**<https://hal.science/hal-03838947v1>**

Submitted on 3 Nov 2022

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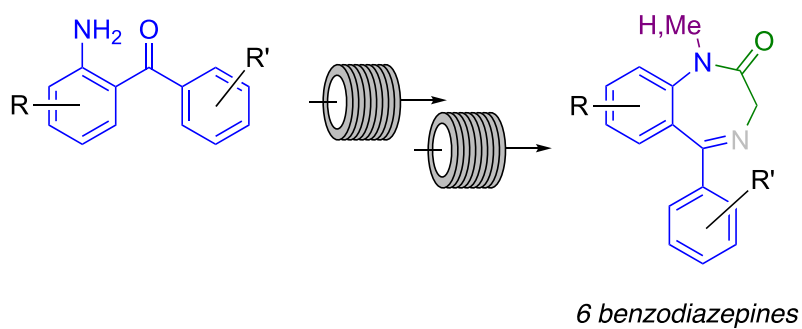
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# Flow platform for the synthesis of benzodiazepines

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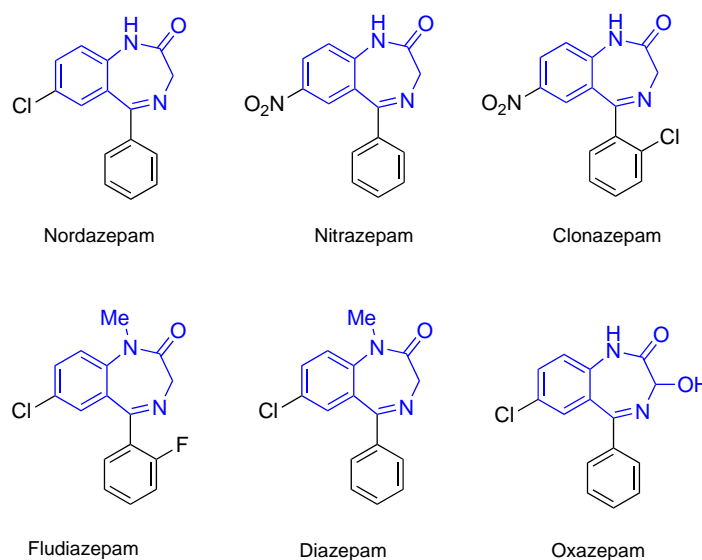
*Please note that Thomas Poisson and Philippe Jubault are also corresponding authors*



**Abstract:** Benzodiazepines possess a wide spectrum of valuable pharmacological effects and are among the leading drugs, commonly prescribed ones for various pathologies. Herein we describe the continuous flow synthesis of six benzodiazepines from aminobenzophenones: diazepam, fludiazepam, nordazepam, nitrazepam, clonazepam, oxazepam.

**Key words:** diazepam, acylation, methylation, oxidation, drugs.

The 1,4-benzodiazepine-2-ones backbone is an essential pharmacophore in the pharmaceutical industry,<sup>1</sup> and the first benzodiazepine was developed in 1960 by Hoffmann-La Roche and marketed as Librium (Scheme 1).<sup>2</sup> This class of compounds exhibits a highly significant clinical activity and finds various therapeutic applications as anxiolytics,<sup>3-7</sup> hypnotic,<sup>8,9</sup> antiarrhythmics,<sup>10</sup> vasopressin antagonists,<sup>11</sup> HIV reverse transcriptase inhibitors,<sup>12</sup> and cholecystokinin antagonists,<sup>13</sup> among others. Some studies even demonstrated the antiproliferative effect of benzodiazepines against cellular tumors.<sup>14</sup> This huge, continuously expanding class, might be as well a key synthon in the synthetic pathways of other fused ring compounds, such as triazolo-, oxadiazolo-, oxazino-, or furanobenzodiazepine, for instance.<sup>15</sup> In spite of the widespread adoption of various dibenzodiazepine scaffolds as molecules possessing psychoactive activity to treat anxiety disorders, the pioneering work of Schmutz in the early 1960s remains to be a significant contribution in the area of the benzodiazepine pharmacophore synthesis.<sup>16-18</sup>

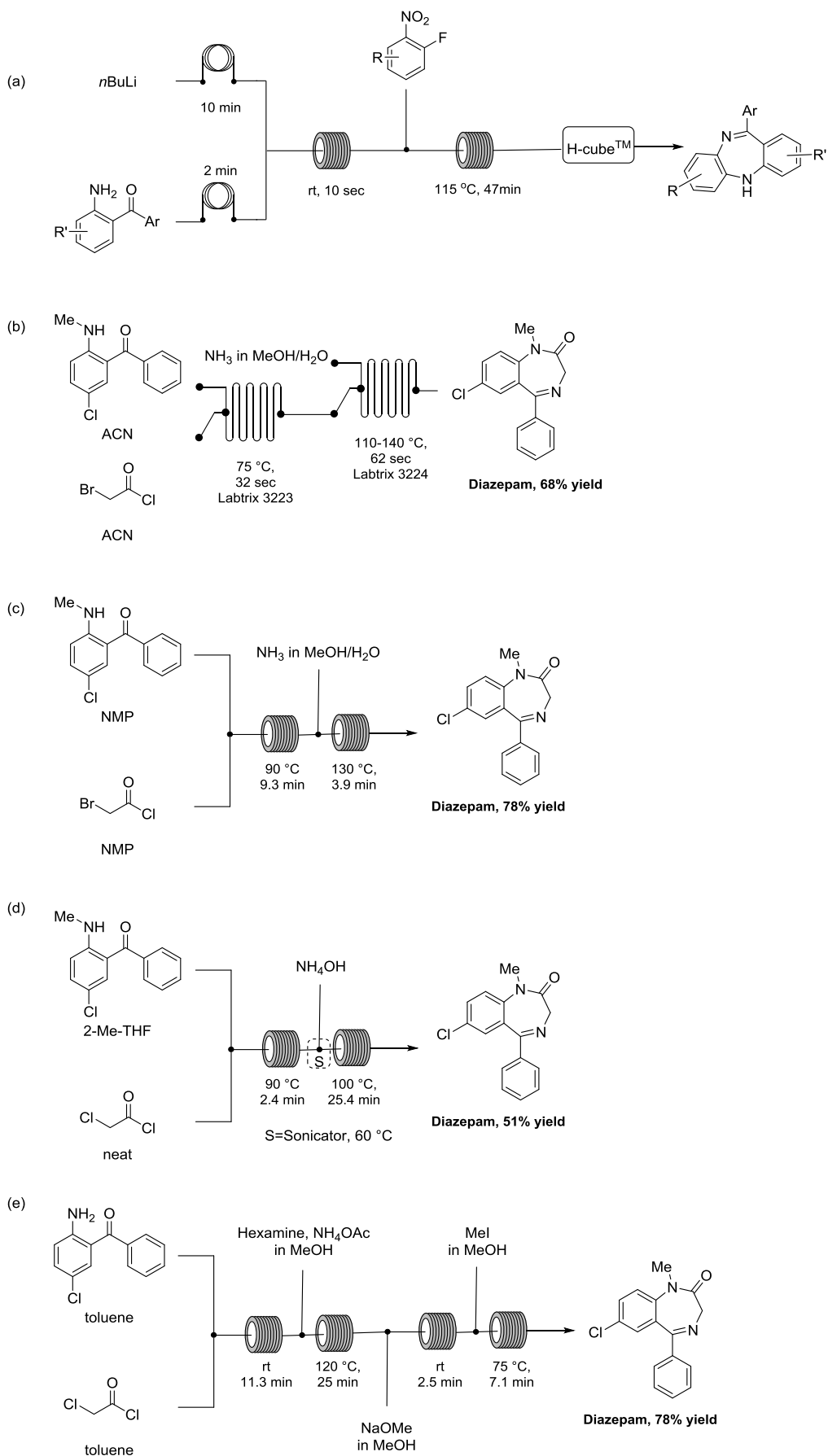


**Scheme 1.** Some relevant examples of benzodiazepines

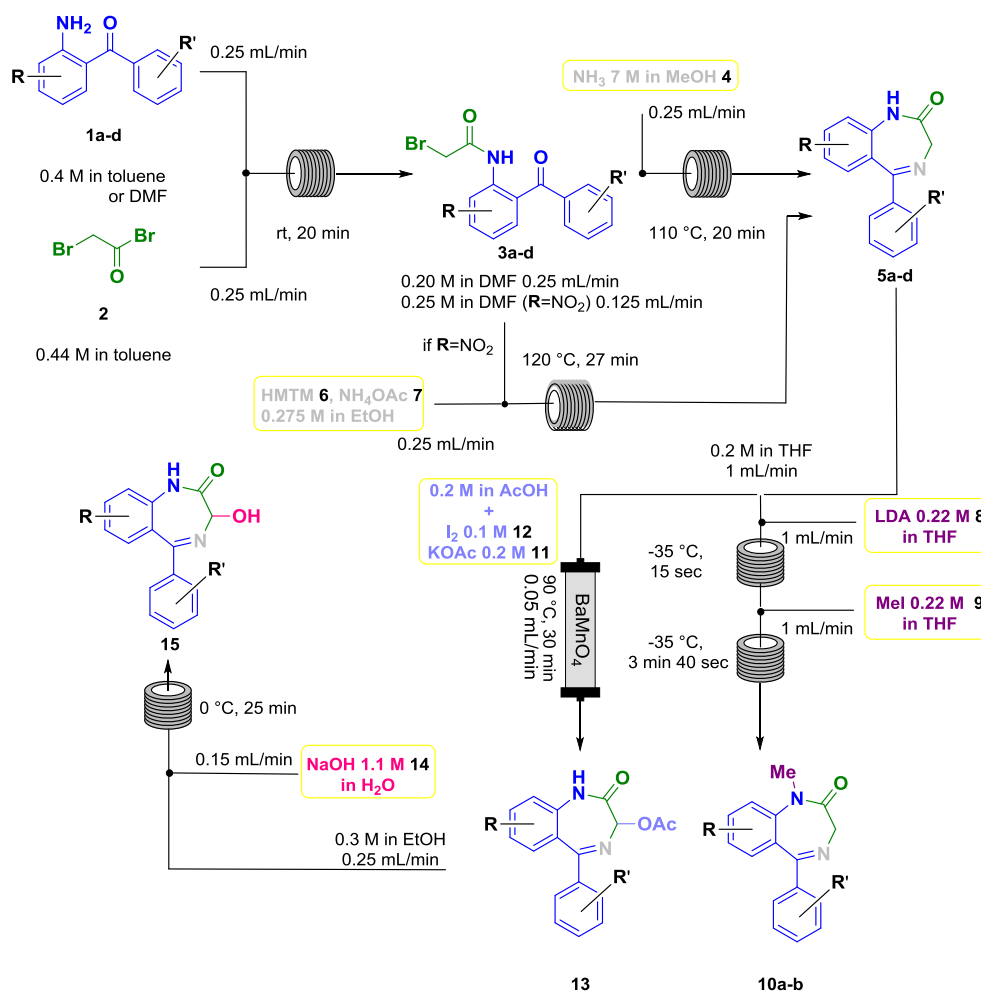
On another hand, continuous flow chemistry is an attractive tool that can allow chemists to access efficiently to highly demanded active pharmaceutical ingredients.<sup>19-25</sup> In this context, the flow synthesis of benzodiazepines has been reported by several groups. Thus, Baxendale described a flow synthesis of benzodiazepines as a combination of a  $S_NAr$  reaction to produce a nitrodiarylamine intermediate, which upon reduction of the nitro group subsequently underwent a cyclocondensation (Scheme 2a).<sup>26</sup> Thompson and colleagues demonstrated the ability of MS analysis and droplet reaction to guide microfluidic synthesis, performing continuous synthesis of diazepam in two steps on a microscale (Scheme 2b).<sup>27</sup> In 2016, the group of Jamison described the preparation of diazepam in flow, starting from the acylation of 5-chloro-2-(methylamino) benzophenone with neat bromoacetyl chloride in NMP, followed by an intramolecular cyclization reaction upon addition of a stream of  $NH_3$

in a MeOH/H<sub>2</sub>O mixture. This method implied an elevated pressure (250 psi) and temperatures (90 °C and 130 °C; Scheme 2c).<sup>28</sup> One year later, the same group depicted a 2-steps process, including the amidation reaction between a solution of benzophenone and neat chloroacetyl chloride, followed by a reaction with aqueous ammonia solution; in-system dilution to avoid clogging and sonicating bath and a static mixer (Scheme 2d).<sup>29</sup> Recently, the report on an automated multistep chemical synthesizer AutoSyn was disclosed, showing the syntheses of ten FDA approved drugs, including diazepam (Scheme 2e).<sup>30</sup> Herein, within the framework of our research program dedicated to the API continuous flow manufacturing,<sup>31,32,33</sup> we describe a general synthesis of 1,4-benzodiazepine-2-one scaffolds. Our flow synthesis of the benzodiazepines is shown in Scheme 2. The installation does not require an additional special equipment or high temperature and allows the access to 6 different benzodiazepines, the largest number of such APIs accessible by a single platform approach reported so far.

**State of the art:**



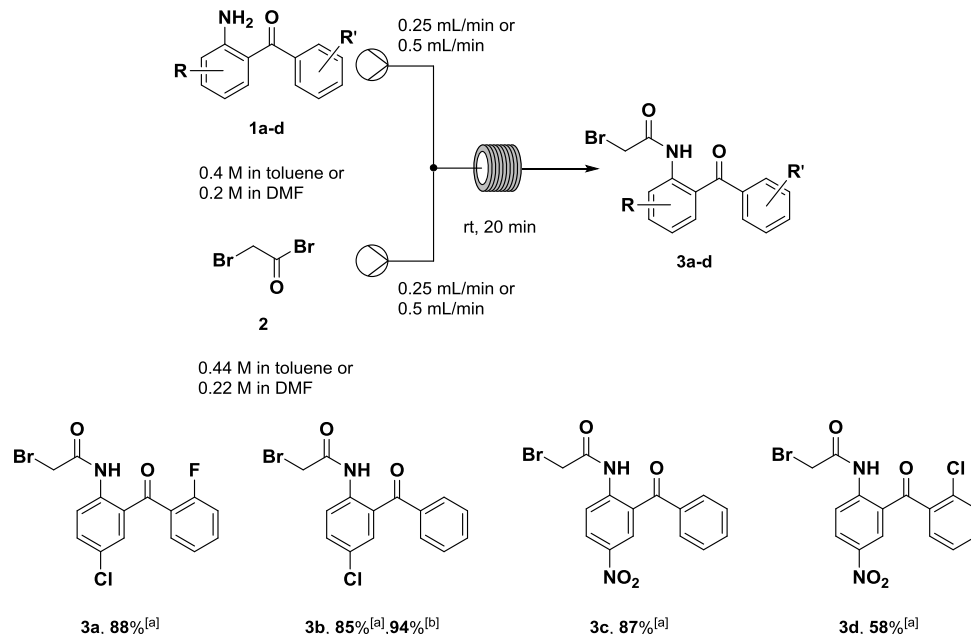
**This work:**



**Scheme 2.** State of the art and present work.

The first step of the synthesis consisted in the formation of *N*-(2-Benzoylphenyl)-2-bromoacetamides **3**, directly starting from the unprotected 2-amino-benzophenone **1** (Scheme 3). 2-Amino-5-chloro-2-fluorobenzophenone **1a** was chosen as a model substrate, in order to facilitate the determination of the conversion of the transformations by <sup>19</sup>F NMR spectroscopy monitoring. The selected compound was diluted in toluene (inlet 1) and then was mixed with a 0.44 M solution of bromoacetyl bromide **2** in toluene (inlet 2), the resulting solution passed through a 10 mL PTFE reactor afterwards. We checked several concentrations of **1** and found that the optimum one was 0.4 M; when working above this value, yield decreased. The excellent conversion and yield were achieved, performing the reaction at room temperature, at the flow rate of 0.25 mL/min of each stream and at the concentration of 0.4 M. The first drop of the solution was furnished after 20 min, while it takes 2 hours to complete this reaction in batch. The product **3a** was formed in 88% yield, calculated on 4 mmol (1.96 g/h, 0.196 kg/h/L) (Scheme 3). Since, the nitro-derivatives **1c-d** are poorly soluble in

toluene, the solvent can be replaced with DMF and the concentration of the starting solution could be reduced by a factor of 2 and the flow rates increased twice, keeping therefore the same productivity and yield.



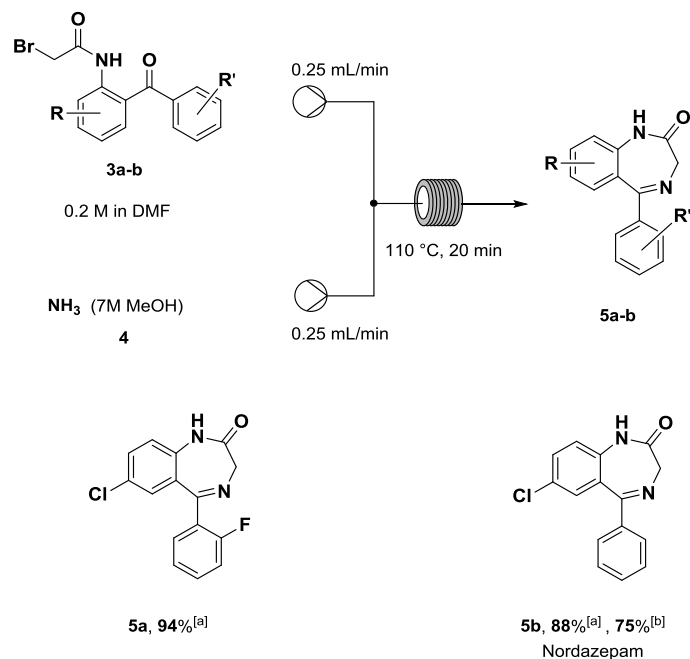
**Scheme 3.** Synthesis of *N*-(2-Benzoylphenyl)-2-bromoacetamides **3a-d** (4 mmol scale). [a] Yield of isolated products. [b] Reaction performed on 24 mmol scale.

To demonstrate the synthetic utility of our process, we performed a reaction on a larger 24 mmol scale with 2-amino-5-chlorobenzophenone **1b**, using Syrris Asia pump, and the corresponding product **3b** was isolated in 94% yield.

Then, to reach the final targets, the acylated products should be subjected to cyclisation, resulting in the formation of 1,4-benzodiazepine-2-ones,<sup>34</sup> and which might then undergo a *N*-methylation or a *C*-acylation,<sup>35</sup> as precursors of various benzodiazepins. The flow system for these transformations was set up using a R-series Vapourtec® flow reactor (R2+ pumps, R4 heater/cooler module) with two pumps. Thus, the next step involved nucleophilic substitution of the bromine by a convenient methanolic solution of NH<sub>3</sub>, followed by the dehydrative cyclisation toward the formation of the benzodiazepine **5**. There was a slight formation of 2-amino-benzophenone **1**, *ie* the starting material of the preceding step, resulting from the transamidification side reaction rather than the bromine substitution (8-24%). We have performed numerous trials to optimize this transformation and avoid the undesired reaction. For instance, we diluted in various ways a commercially available 7 M solution of NH<sub>3</sub> in MeOH, but it did not influence the outcome of the reaction. Pleasingly, the ratio product/byproduct increased according to the temperature from 30 to 110 °C, whereas exceeding the latter resulted in lower yield. It was also preferable to use a larger reactor (10 mL) with a fast flow

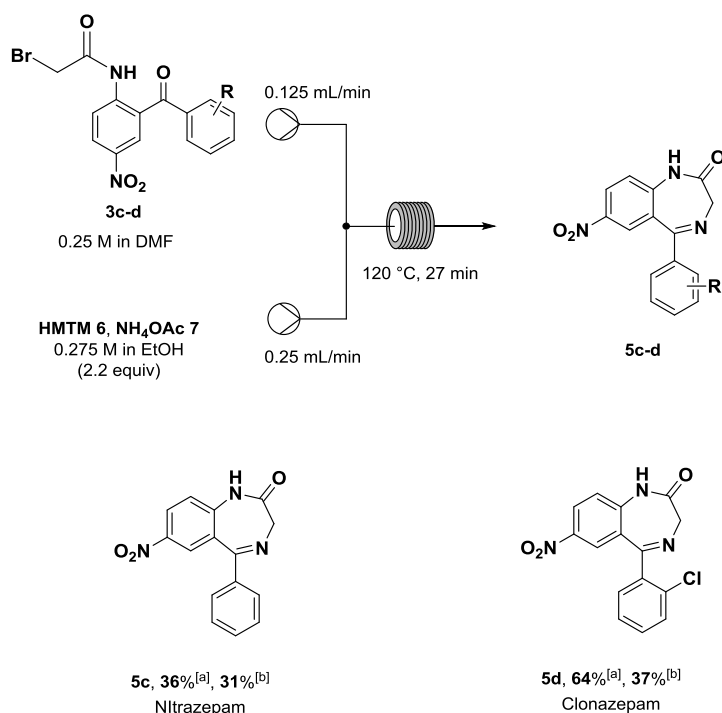


rate, rather than a small reactor (2-5 mL) along with a low flow rate. The total flow rate of 0.5 mL/min (0.25 mL/min + 0.25 mL/min) was the most beneficial ( $t^R = 20$  min). DMF was superior to toluene and 1,4-dioxane, and the maximum concentration of the substrate was 0.2 M in DMF. The solutions of ammonia in different solvents were also tried, among 7 M methanol, 0.4 M THF, 2 M ethanol, the former gave the best results. The reaction was performed on 4 mmol scale and the product **5a** was obtained in a very good 94% yield (0.814 g/h, 0.081 kg/h/L) (Scheme 4).



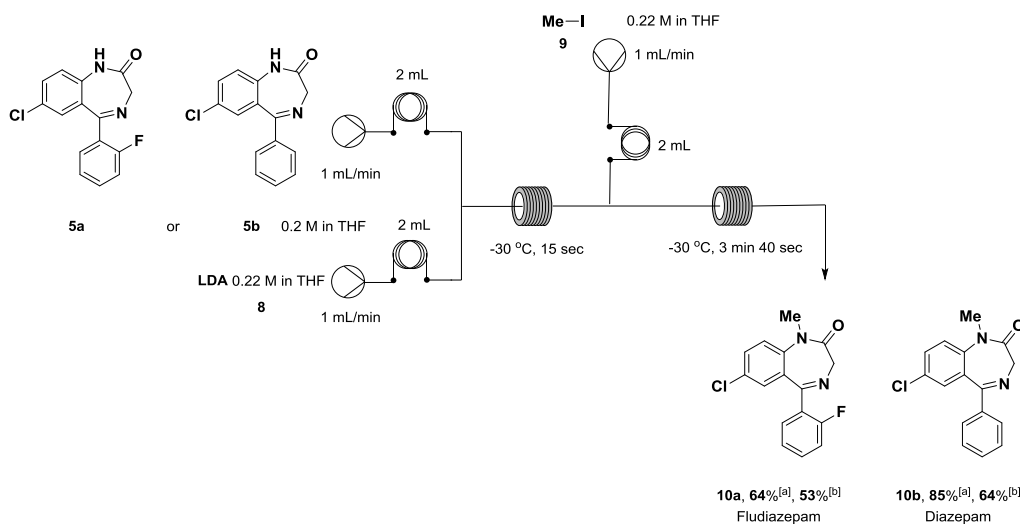
**Scheme 4.** Formation of benzodiazepines using  $\text{NH}_3$  in MeOH (4 mmol scale). [a] Yield of isolated products. [b] Overall yield.

Alternatively, since the above-mentioned method was ineffective for the nitro-derivatives **3c-d**, we applied the hexamethylenetetramine/ammonium acetate **6/7** system (Scheme 5). A 0.25 M solution of *N*-(2-Benzoylphenyl)-2-bromoacetamide **3c-d** in DMF was combined within the T-piece of the R2/R4 unit with a second stream containing HMTM **6** and  $\text{NH}_4\text{OAc}$  **7** (0.275 M in EtOH) at the flow rates of 0.125 mL/min and 0.25 mL/min, respectively. The united stream was then directed into a PTFE reactor (10 mL) at 120 °C, ( $t^R = 27$  min), the Nitrazepam **5c** was obtained in a modest 36% yield (0.190 g/h, 0.019 kg/h/L) (Scheme 4). Note that the overall yield of the nitrazepam was 31% over 2 steps. Finally, this protocol was applied to the synthesis of clonazepam **5d**, which was isolated in a good 64% yield and a 37% yield over 2 steps.



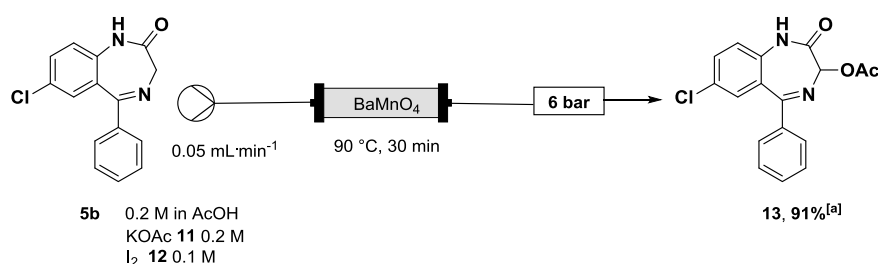
**Scheme 5.** Synthesis of nitrazepam and clonazepam using HMTM/NH<sub>4</sub>OAc (2 mmol scale). [a] Yield of isolated products. [b] Overall yield.

With the goal to carry out efficiently the *N*-alkylation of the obtained heterocycles, we examined many conditions, which could be readily applied in flow chemistry. A small part of what we tried comprises Me<sub>2</sub>SO<sub>4</sub>/K<sub>2</sub>CO<sub>3</sub> neat, Me<sub>2</sub>SO<sub>4</sub>/*t*-BuOK/CH<sub>3</sub>CN, MeOTf, MeO<sup>+</sup>BF<sub>4</sub><sup>-</sup>, Me<sub>2</sub>SO<sub>4</sub> neat, NaH/methylating agent, LDA/methylating agent, *n*BuLi/methylating agent at different temperatures, ratios and solvents. The results were ranged from bad to moderately good, especially, LDA/MeI was remarkable at low temperatures. After further investigations, we were finally satisfied with the conversion and yield and turned our attention to conditions in flow. Three syringes were loaded with 3 solutions : benzodiazepine **5a-b** in dry THF (0.2 M), LDA **8** freshly prepared and MeI **9**, both at 0.22 M in dry THF. The two first solutions were simultaneously passed through two 2 mL pre-cooling loops at -35 °C both at a 1 mL/min flow rate and were combined within a T-mixer. Then, the flow passed a 0.5 mL reactor at -35 °C, and then it was combined with a flow of the electrophile, which was pre-cooled as well at -35 °C by passing through a 2 mL pre-cooling loop at 1 mL/min. Eventually the combined solution was directed in a 11 mL reactor. The total residence time of this reaction came up to (15 sec + 3 min 40 sec) 3 min 55 sec. The solution was finally quenched with the solution of ammonia chloride, extracted with EtOAc and after a simple column, the product **10a** was obtained in 64% yield, based on 0.8 mmol scale (2.33 g/h, 0.2 kg/h/L, Scheme 6).



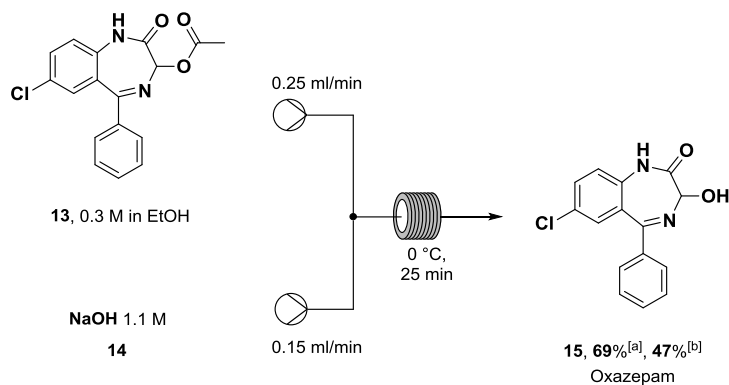
**Scheme 6.** Synthesis of fludiazepam and diazepam through *N*-alkylation of benzodiazepines (0.8 mmol scale). [a] Yield of isolated products. [b] Overall yield.

From the class of 3-hydroxy-1,4-benzodiazepines, oxazepam **15** and lorazepam are widely used for the treatment of anxiety.<sup>36</sup> To synthesize 3-hydroxy derivatives of 1,4-benzodiazepines, first of all it is necessary to address the direct acetoxylation of the 3 position of the benzodiazepine backbone. As an oxidant we aimed at finding one, which could easily fill in a column reactor and not create a clogging. Among  $K_2S_2O_8$ ,  $NaNO_2$ ,  $MnO_2$  and  $BaMnO_4$ , the latter was the easiest to deal with. The solution of benzodiazepine **5b**, iodine **12**, KOAc **11** in acetic acid (0.2 M) was flowed through a column reactor heated at 90 °C at 0.05 mL/min, the column was filled with mixture of  $BaMnO_4$  (2 equiv) and silica (1 g total). The residence time of the transformation was 30 min, after that the solution was diluted with EtOAc, washed with the solutions of sodium thiosulfate and bicarbonate, extracted with EtOAc, passed through a shot plug of silica and evaporated, the product **13** was obtained in an excellent yield 91%, based on 2 mmol scale (0.18 g/h) (Scheme 7).



**Scheme 7.** Acetoxylation reaction of the 3-position of the 1,4-benzodiazepine ring (2 mmol scale). [a] Yield of isolated product.

The obtained product **13** was converted by basic ester hydrolysis at 0 °C, followed by acidification with AcOH, into oxazepam **15**, in a yield of 69%, based on 0.5 mmol scale (0.89 g/h, 0.089 kg/h/L; Scheme 8).



**Scheme 8.** Hydrolysis of **13** into oxazepam (0.5 mmol scale). [a] Yield of isolated product. [b] Overall yield.

## Conclusion

To conclude, robust flow chemical routes towards the valuable bioactive entities 1,4-benzodiazepine-2-ones has described. The protocol needs minimum requirements and could be applied for a great number of starting materials, providing a reliable route to this vital class of compounds. The use of flow chemistry translated to increased safety and shorter processing times. On a global standpoint, we performed the complete syntheses of 6 important 1,4-benzodiazepine-2-ones, with overall yields ranging from 31 to 75%. In the current post-pandemic situation, these syntheses offer a straightforward platform for the continuous flow synthesis of strategic entities 1,4-benzodiazepine-2-ones.

## Acknowledgements

This work is part of the API program supported by the European Union through the operational program FEDER/FSE 2014–2020 (no. 20E04976) and FNADT-DRACCARE program 2020–2023 ((N)15179). This work has been partially supported by University of Rouen Normandy, INSA Rouen Normandy, the Centre National de la Recherche Scientifique (CNRS), European Development Fund (ERDF), Labex SynOrg (ANR-11-LABX-0029), Carnot Institute I2C, the graduate school for research XL-Chem (ANR-18-EURE-0020 XL CHEM), and by Région Normandie. T.P. thanks the Institut Universitaire de France (IUF) for support.

## References

- (1) Archer, G. A.; Sternbach, L. H. Chemistry of Benzodiazepines. *Chem. Rev.* **1968**, *68*, 747–784.
- (2) Sternbach, L. H. The Benzodiazepine Story. *J. Med. Chem.* **1979**, *22*, 1–7.
- (3) Wright, W. B.; Brabander, H. J.; Greenblatt, E. N.; Day, I. P.; Hardy, R. A. Derivatives of 1,2,3,11a-Tetrahydro-5H-Pyrrolo[2,1-c][1,4]Benzodiazepine-5,11(10H)-Dione as Anxiolytic Agents. *J. Med. Chem.* **1978**, *21*, 1087–1089.
- (4) Reddy, S.; Patt, R. B. The Benzodiazepines as Adjuvant Analgesics. *J. Pain Symptom Manage.* **1994**, *9*, 510–514.
- (5) Lattmann, E.; Lattmann, P.; Boonprakob, Y.; Airarat, W.; Singh, H.; Offel, M.; Sattayasai, J. In Vivo Evaluation of Substituted 3-Amino-1,4-Benzodiazepines as Anti-Depressant, Anxiolytic and Anti-Nociceptive Agents. *Arzneimittelforschung* **2009**, *59*, 61–71.
- (6) Möhler, H.; Okada, T. Benzodiazepine Receptor: Demonstration in the Central Nervous System. *Science* **1977**, *198*, 849–851.
- (7) Shorter, E. *A Historical Dictionary of Psychiatry*; Oxford University Press, 2005.
- (8) Hallahan, B. P.; Murray, I. T.; McDonald, C. Benzodiazepine and Hypnotic Prescribing in an Acute Adult Psychiatric In-Patient Unit. *Psychiatr. Bull.* **2009**, *33*, 12–14.
- (9) Scharf, M. B.; Fletcher, K.; Graham, J. P. Comparative Amnestic Effects of Benzodiazepine Hypnotic Agents. *J. Clin. Psychiatry* **1988**, *49*, 134–137.
- (10) Selnick, H. G.; Liverton, N. J.; Baldwin, J. J.; Butcher, J. W.; Claremon, D. A.; Elliott, J. M.; Freidinger, R. M.; King, S. A.; Libby, B. E.; McIntyre, C. J.; Pribush, D. A.; Remy, D. C.; Smith, G. R.; Tebben, A. J.; Jurkiewicz, N. K.; Lynch, J. J.; Salata, J. J.; Sanguinetti, M. C.; Siegl, P. K. S.; Slaughter, D. E.; Vyas, K. Class III Antiarrhythmic Activity in Vivo by Selective Blockade of the Slowly Activating Cardiac Delayed Rectifier Potassium Current IKs by (R)-2-(2,4-Trifluoromethyl)-N-[2-Oxo-5-Phenyl-1-(2,2,2-Trifluoroethyl)-2,3-Dihydro-1H-Benzo[e][1,4]Diazepin-3-Yl]Acetamide. *J. Med. Chem.* **1997**, *40*, 3865–3868.
- (11) Albright, J. D.; Reich, M. F.; Delos Santos, E. G.; Dusza, J. P.; Sum, F.-W.; Venkatesan, A. M.; Coupet, J.; Chan, P. S.; Ru, X.; Mazandarani, H.; Bailey, T. 5-Fluoro-2-Methyl-N-[4-(5H-Pyrrolo[2,1-c]-[1,4]Benzodiazepin-10(11H)-Ylcarbonyl)-3-Chlorophenyl]Benzamide (VPA-985): An Orally Active Arginine Vasopressin Antagonist with Selectivity for V2 Receptors. *J. Med. Chem.* **1998**, *41*, 2442–2444.
- (12) Breslin, H. J.; Kukla, M. J.; Ludovici, D. W.; Mohrbacher, R.; Ho, W.; Miranda, M.; Rodgers, J. D.; Hitchens, T. K.; Leo, G. Synthesis and Anti-HIV-1 Activity of 4,5,6,7-Tetrahydro-5-Methylimidazo[4,5,1-jk][1,4]Benzodiazepin-2(1H)-One (TIBO) Derivatives. 3. *J. Med. Chem.* **1995**, *38*, 771–793.
- (13) Castro, J. L.; Broughton, H. B.; Russell, M. G. N.; Rathbone, D.; Watt, A. P.; Ball, R. G.; Chapman, K. L.; Patel, S.; Smith, A. J.; Marshall, G. R.; Matassa, V. G. 5-(Piperidin-2-Yl)- and 5-(Homopiperidin-2-Yl)-1,4-Benzodiazepines: High-Affinity, Basic Ligands for the Cholecystokinin-B Receptor. *J. Med. Chem.* **1997**, *40*, 2491–2501.
- (14) Doulat, J.; Liu, W.-Q.; Gresh, N.; Garbay, C. Novel 1,4-Benzodiazepine Derivatives with

Antiproliferative Properties on Tumor Cell Lines. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 2527–2530.

(15) Insuasty, B.; Garcia, A.; Quiroga, J.; Abonia, R.; Nogueras, M.; Cobo, J. ChemInform Abstract: Synthesis of Novel 6,6a,7,8-Tetrahydro-5H-Naphtho[1,2-e]Pyrimido[4,5-b][1,4]Diazepines under Microwave Irradiation as Potential Antitumor Agents. *ChemInform* **2010**, *41*, 2841–2846.

(16) Hunziker, F.; Künzle, F.; Schindler, O.; Schmutz, J. Dibenzo-Azepine, -Diazepine, -Oxazepine Und -Thiazepine. 3. Mitteilung Über Siebengliedrige Heterocyclen. *Helv. Chim. Acta* **1964**, *47*, 1163–1172.

(17) Hunziker, F.; Fischer, E.; Schmutz, J. 11-Amino-5H-Dibenzo[b, e]-1, 4-Diazepine. 10. Mitteilung Über Siebengliedrige Heterocyclen. *Helv. Chim. Acta* **1967**, *50*, 1588–1599.

(18) Schmutz, J.; Künzle, F.; Hunziker, F.; Gauch, R. Über in 11-Stellung Amino-Substituierte Dibenzo[b,f]-1, 4-Thiazepine Und -Oxazepine. 9. Mitteilung Über Siebengliedrige Heterocyclen. *Helv. Chim. Acta* **1967**, *50*, 245–254.

(19) Domokos, A.; Nagy, B.; Szilágyi, B.; Marosi, G.; Nagy, Z. K. Integrated Continuous Pharmaceutical Technologies—A Review. *Org. Process Res. Dev.* **2021**, *25* (4), 721–739. <https://doi.org/10.1021/acs.oprd.0c00504>.

(20) Hughes, D. L. Applications of Flow Chemistry in the Pharmaceutical Industry—Highlights of the Recent Patent Literature. *Org. Process Res. Dev.* **2020**, *24* (10), 1850–1860. <https://doi.org/10.1021/acs.oprd.0c00156>.

(21) Gioiello, A.; Piccinno, A.; Lozza, A. M.; Cerra, B. The Medicinal Chemistry in the Era of Machines and Automation: Recent Advances in Continuous Flow Technology. *J. Med. Chem.* **2020**, *63* (13), 6624–6647. <https://doi.org/10.1021/acs.jmedchem.9b01956>.

(22) Ferlin, F.; Lanari, D.; Vaccaro, L. Sustainable Flow Approaches to Active Pharmaceutical Ingredients. *Green Chem.* **2020**, *22* (18), 5937–5955. <https://doi.org/10.1039/D0GC02404J>.

(23) Bloemendal, V. R. L. J.; Janssen, M. A. C. H.; Hest, J. C. M. van; Rutjes, F. P. J. T. Continuous One-Flow Multi-Step Synthesis of Active Pharmaceutical Ingredients. *React. Chem. Eng.* **2020**, *5* (7), 1186–1197. <https://doi.org/10.1039/D0RE00087F>.

(24) Gérardy, R.; Emmanuel, N.; Toupy, T.; Kassin, V.-E.; Tshibalonza, N. N.; Schmitz, M.; Monbaliu, J.-C. M. Continuous Flow Organic Chemistry: Successes and Pitfalls at the Interface with Current Societal Challenges: Continuous Flow Organic Chemistry: Successes and Pitfalls at the Interface with Current Societal Challenges. *Eur. J. Org. Chem.* **2018**, *2018* (20–21), 2301–2351. <https://doi.org/10.1002/ejoc.201800149>.

(25) De Angelis, S.; Celestini, P.; Purgatorio, R.; Degennaro, L.; Rebuzzini, G.; Luisi, R.; Carlucci, C. Development of a Continuous Flow Synthesis of Propranolol: Tackling a Competitive Side Reaction. *J. Flow Chem.* **2019**, *9* (4), 231–236. <https://doi.org/10.1007/s41981-019-00047-8>.

(26) Baumann, M.; Baxendale, I. R.; Hornung, C. H.; Ley, S. V.; Rojo, M. V.; Roper, K. A. Synthesis of Riboflavines, Quinoxalinones and Benzodiazepines through Chemoselective Flow Based Hydrogenations. *Molecules* **2014**, *19*, 9736–9759.

(27) Ewan, H. S.; Iyer, K.; Hyun, S.-H.; Wleklinski, M.; Cooks, R. G.; Thompson, D. H. Multistep Flow Synthesis of Diazepam Guided by Droplet-Accelerated Reaction Screening with Mechanistic Insights from Rapid Mass Spectrometry Analysis. *Org. Process Res. Dev.* **2017**, *21* (10), 1566–1570. <https://doi.org/10.1021/acs.oprd.7b00218>.

(28) Adamo, A.; Beingessner, R. L.; Behnam, M.; Chen, J.; Jamison, T. F.; Jensen, K. F.; Monbaliu, J.-C. M.; Myerson, A. S.; Revalor, E. M.; Snead, D. R.; Stelzer, T.; Weeranoppanant, N.;

- Wong, S. Y.; Zhang, P. On-Demand Continuous-Flow Production of Pharmaceuticals in a Compact, Reconfigurable System. *Science* **2016**, *352*, 61–67.
- (29) Bédard, A.-C.; Longstreet, A. R.; Britton, J.; Wang, Y.; Moriguchi, H.; Hicklin, R. W.; Green, W. H.; Jamison, T. F. Minimizing E-Factor in the Continuous-Flow Synthesis of Diazepam and Atropine. *Bioorg. Med. Chem.* **2017**, *25*, 6233–6241.
- (30) Collins, N.; Stout, D.; Lim, J.-P.; Malerich, J. P.; White, J. D.; Madrid, P. B.; Latendresse, M.; Krieger, D.; Szeto, J.; Vu, V.-A.; Rucker, K.; Deleo, M.; Gorf, Y.; Krummenacker, M.; Hokama, L. A.; Karp, P.; Mallya, S. Fully Automated Chemical Synthesis: Toward the Universal Synthesizer. *Org. Process Res. Dev.* **2020**, *24*, 2064–2077.
- (31) Mougeot, R.; Jubault, P.; Legros, J.; Poisson, T. Continuous Flow Synthesis of Propofol. *Molecules* **2021**, *26*, 7183.
- (32) Ivanova, M.; Legros, J.; Poisson, T.; Jubault, P. Continuous Flow Synthesis of Celecoxib from 2-Bromo-3,3,3-Trifluoropropene. *J. Flow Chem.* **2021**.
- (33) Desrues, T.; Legros, J.; Jubault, P.; Poisson, T. Flow Synthesis of an  $\alpha$ -Amino Boronic Ester as a Key Precursor of Bortezomib Drug. *React. Chem. Eng.* **2022**, *7* (6), 1285–1288.
- (34) Blažević, N.; Kajfež, F. A New Ring Closure of 1,4-Benzodiazepine. *J. Heterocycl. Chem.* **1970**, *7*, 1173–1174.
- (35) Capanec, I.; Litvić, M.; Pogorelić, I. Efficient Synthesis of 3-Hydroxy-1,4-Benzodiazepines Oxazepam and Lorazepam by New Acetoxylation Reaction of 3-Position of 1,4-Benzodiazepine Ring. *Org. Process Res. Dev.* **2006**, *10*, 1192–1198.
- (36) Biyani, S. A.; Lytle, C.; Hyun, S.-H.; McGuire, M. A.; Pendyala, R.; Thompson, D. H. Development of a Continuous Flow Synthesis of Lorazepam. *Org. Process Res. Dev.* **2022**. <https://doi.org/10.1021/acs.oprd.2c00184>.