A Journal of the Gesellschaft Deutscher Chemiker

Angewandte International Edition Chemie

GDCh

www.angewandte.org

Accepted Article

Title: Integration of Bromine and Cyanogen Bromide Generators for the Telescoped Continuous Synthesis of Cyclic Guanidines

Authors: Gabriel Glotz, Rene Lebl, Doris Dallinger, and C. Oliver Kappe

To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.201708533
Angew. Chem. 10.1002/ange.201708533

Link to VoR: http://dx.doi.org/10.1002/anie.201708533
http://dx.doi.org/10.1002/ange.201708533

WILEY-VCH

10.1002/anie.201708533

WILEY-VCH

Integration of Bromine and Cyanogen Bromide Generators for the Telescoped Continuous Synthesis of Cyclic Guanidines

Gabriel Glotz,[a,b] René Lebl,[a,b] Doris Dallinger,[b] and C. Oliver Kappe*[a,b]

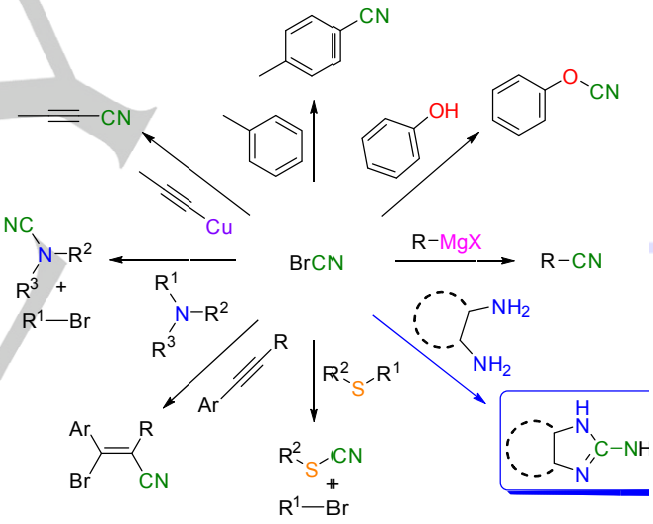
Dedicated to Professor Albert Padwa on the occasion of this 80th birthday

Abstract: A continuous flow process for the in-situ on-demand generation of cyanogen bromide (BrCN) from bromine and potassium cyanide utilizing membrane separation technology is described. In order to circumvent handling, storage and transportation of elemental bromine, a continuous bromine generator using bromate-bromide synproportionation can optionally be attached upstream. Monitoring and quantification of BrCN generation was enabled by implementation of in-line FTIR technology. With the Br_2 and BrCN generators connected in series 0.2 mmol BrCN per minute was produced corresponding to a 0.8 M solution of BrCN in dichloromethane. The modular Br_2/BrCN generator has been employed for the synthesis of a diverse set of biologically relevant five- and six-membered cyclic amidines and guanidines. The set-up can either be operated in a fully integrated continuous format or, where reactive crystallization is beneficial, in semi-batch mode.

To eliminate the need of handling, storage and transportation of toxic, reactive, or explosive reagents these materials are best produced when needed from benign precursors directly at the site of use. The in-situ synthesized reagent is then directly converted into the desired product. Continuous flow processing specifically addresses the needs for this so-called “on-site on-demand” generation of hazardous species with safety being one of the most significant advantages over a traditional batch set-up.[1] Inside a low volume reactor, the accumulation of dangerous amounts of hazardous materials is avoided since only small quantities are present at any time. In addition, rapid exothermic reactions can safely be performed due to the high mass- and heat transfer rates.[1]

Set-ups for the continuous production of synthetically useful reagents are commonly termed “generators” of the reagent.[2] In an ideal scenario the complete operation including generation of the reagent, its separation and downstream consumption is performed in a fully contained fashion ensuring zero exposure to the hazardous material throughout operation.[2,3] Several continuous generators of highly reactive and/or hazardous/toxic reagents following these principles have been reported in recent years.[2-9]

A significant part of our current research is directed toward developing new methodology and to broaden the scope of the chemical generator concept. In this context, cyanogen bromide (BrCN) is an interesting target molecule: it is an exceptionally versatile reagent in organic synthesis[10,11] which most frequently participates as an electrophilic cyanide source and reacts with N O, S, C and P nucleophiles to generate e.g. cyanamides,[12] guanidines,[13] cyanates[14] or nitriles[15] (Scheme 1). In addition, it can be used in the von Braun reaction for the dealkylation of tertiary amines which often results in ring-opening of the respective N-heterocycles.[10,16,17] Along similar lines, BrCN can also act as a cleavage agent for dialkyl thioethers.[18] This reaction represents an important technique in peptide mapping and amino acid sequence analysis, due to the regioselective demethylation of methionine-containing peptides.[10,11,19] Notably, bromocyanation of alkynes with BrCN provides the most atom-efficient method for the synthesis of bromoacrylonitriles.[20]



Scheme 1. Synthetic versatility of BrCN.

However, BrCN has to be classified as a very hazardous chemical. It is acutely toxic, it sublimes at room temperature and can be absorbed into the body by inhalation of its vapor and through the skin.[21] Exposure to even small amounts may cause convulsions or death.[22] Pure BrCN is stable for longer periods if stored under dry conditions at 2-8 °C, but impurities catalyze its exothermic and explosive trimerization to cyanuric bromide. Furthermore, it is gradually decomposed by water/moisture and rapidly by acids to highly toxic HCN and corrosive HBr. Although BrCN is commercially available, it would clearly be desirable to avoid its transportation, storage and handling. We have therefore developed a BrCN generator for on-site on-demand usage that produces this material from aqueous Br_2 and KCN solutions in a continuous flow format (Figure 1). A solution of pure BrCN was obtained after in-line liquid/liquid separation and

[a] G. Glotz, R. Lebl, Prof. Dr. C. Oliver Kappe
Center for Continuous Flow Synthesis and Processing (CC FLOW),
Research Center Pharmaceutical Engineering GmbH (RCPE)
Inffeldgasse 13, 8010 Graz (Austria)
E-mail: oliver.kappe@uni-graz.at
Homepage: http://goflow.at/
[b] G. Glotz, R. Lebl, Dr. D. Dallinger, Prof. Dr. C. Oliver Kappe
Institute of Chemistry, NAWI Graz, University of Graz
Heinrichstrasse 28, 8010 Graz (Austria)

Supporting information for this article is given via a link at the end of the document.

immediately used for further downstream transformations in a fully continuous and telescoped strategy. To start the synthetic sequence from truly benign reagents, a Br_2 generator was additionally developed that can act either as stand-alone module for performing brominations or be directly coupled to the BrCN generator upstream supplying the Br_2 feed.

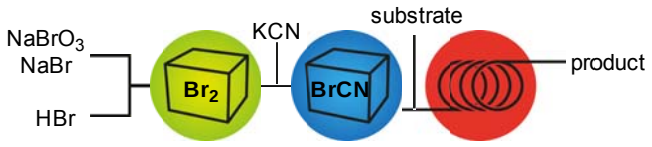


Figure 1. Concept for in-series connected Br_2 and BrCN generators.

In the traditional batch synthesis of BrCN from NaCN or KCN and Br_2 carried out in aqueous solution at 0-30 °C pure BrCN can be obtained via distillation (bp 61-62 °C) in 73-90% yield.[23] For our BrCN generator a continuous in-line extraction of the formed BrCN from the aqueous into an organic phase appeared to be the most appropriate purification technique. Initial studies therefore commenced with an evaluation of the separation performance of the Zaiput liquid-liquid membrane separator[24] with respect to different pore-sized membranes and organic solvents (see Table S1 and Figure S1). Optimum separation results were achieved using DCM as extraction solvent and a 0.5 µm pore size membrane. In order to determine the concentration of BrCN in the organic stream after extraction, a calibration curve of BrCN in DCM was recorded implementing in-line FTIR spectroscopy (ReactIR)[25] to monitor the characteristic CN stretch at 2188 cm^{-1} (see Figures S2, S3).

Next, we focused on the continuous generation of BrCN from KCN and Br_2 with an integrated extraction procedure (Figure 2). To attain a sufficiently concentrated homogeneous solution of Br_2 in water, KBr was added to increase the solubility of Br_2 (1 M Br_2 in 13% aq KBr).[26] Since the reaction of Br_2 with KCN is highly exothermic both feeds were pre-cooled in an ice-bath before mixing and entering the reaction coil (also cooled in the ice-bath). For separation, the aqueous mixture exiting the reaction coil was combined with DCM in a glass microreactor chip (250 µL, 20 s residence time) and directed into the Zaiput extraction unit.

Figure 2. BrCN generator set-up. Feed A: 1 M Br_2 in 13% aq KBr, 250 µL min^{-1}; feed B: 1.15 M aq KCN, 250 µL min^{-1}; PFA coil (0.8 mm i.d.) at 0-5 °C: 5.2 min residence time; feed C: DCM, 250 µL min^{-1}; glass microreactor chip: 20 s residence time; liquid/liquid separator; FTIR. For more details, see Figures S4-S6.

The separated organic stream containing pure BrCN was finally fed into the flow cell of the FTIR in order to determine the concentration/yield of BrCN. In addition, FTIR was useful for assessing the extraction efficiency by monitoring the water OH stretch around 3500 cm^{-1} in the organic feed, corroborating the superior performance of a 0.5 µm pore size hydrophobic membrane (see Figure 3). Optimum results were obtained using a residence time of 5.2 min in the BrCN generating coil resulting in a 0.72 M solution (72% yield based on Br_2) of BrCN in DCM (see Table S2 and Figure S7).

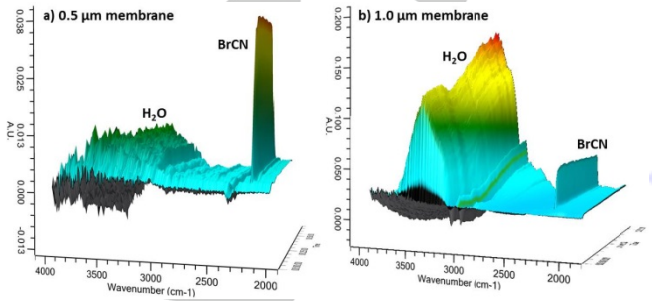


Figure 3. FTIR 3-D surface images of the organic feed after extraction using the Zaiput separator with a hydrophobic membrane of 0.5 µm (a) and 1.0 µm (b) pore size.

With the BrCN generator in hand, our attention shifted toward the downstream chemistry. We decided to investigate the synthesis of cyclic guanidines and structurally related heterocycles using BrCN as cyclization reagent (Figure 4). Molecules containing the guanidine structural motif have emerged as important pharmacophores in biomedical research,[27] a recent example being verubecestat for the treatment of Alzheimer's disease where the use of BrCN has been shown to be essential.[28] As model reaction for optimization studies the condensation of *o*-phenylenediamine with BrCN was selected to provide 2-aminobenzimidazole **1a** as HBr salt. To suppress precipitation of the HBr salt in DCM, the substrate was dissolved in MeOH and then combined with the BrCN stream from the generator. By adjusting the flow rate of the substrate feed, different substrate:BrCN ratios could easily be screened: a small excess of 1.16 equiv of BrCN provided full conversion to **1a** at 50 °C and 25 min residence time. After a simple evaporation and filtration sequence, **1a** could be isolated in 92% yield. By applying these optimized conditions a set of 5-membered cyclic guanidines **1a-d** and 2-aminobenzoxazoles **2a-g**, respectively, was synthesized in excellent yields (80-94%) from the corresponding 1,2-diaminobenzens and 2-aminophenols (Figure 4). To also access the medicinally interesting cyclic 6-membered guanidine moiety,[27,28] 1,3-diamines and 2-aminobenzamides were reacted with BrCN to generate cyclic guanidines **1f-n**. Compound **1k**, for example, was recently synthesized and assayed as a potential HCV (hepatitis C virus) translation inhibitor.[29] Although HPLC conversions were generally ≥90%, side product formation was experienced in all cases and either column chromatography or silica plug filtration was necessary to obtain the pure guanidines **1f-n** in moderate to good yields (41-87%). Apart from the condensed guanidines, 2-amino-*N*-phenyl-imidazoline **1e**, an

10.1002/anie.201708533

intermediate in the synthesis of an antifungal agent, was successfully synthesized (79%).[30]

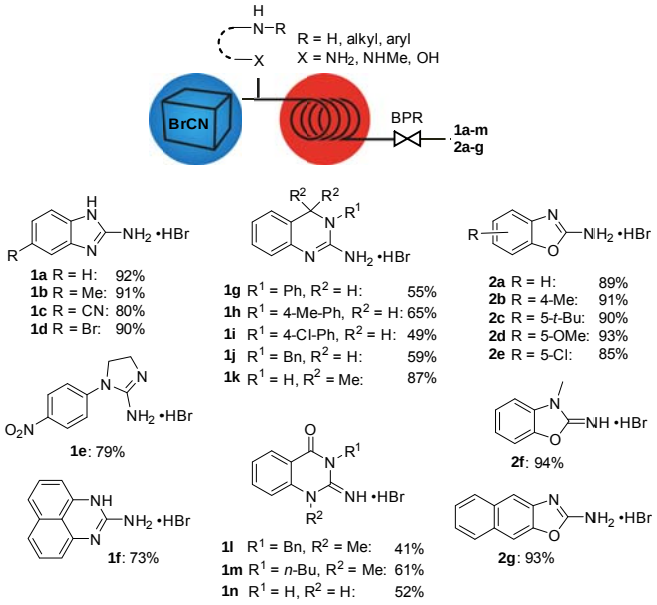


Figure 4. Synthesis of cyclic guanidines and 2-aminobenzoxazoles. Feed A: 0.7 M BrCN in DCM, 250 µL min^{-1}; feed B: 1 M substrate in MeOH, 150 µL min^{-1}; substrate:BrCN (1:1.16); PFA coil (0.8 mm i.d.) at 50 °C, 25 min residence time; back pressure regulator (BPR): 2 bar. For more details on the experimental procedures and set-up see the Supporting Information and Figure S10.

An additional measure to increase the safety level of the overall process would also incorporate a continuous generation of Br_2, since its use likewise presents a serious hazard (volatile, corrosive, irritating, toxic) and precautionary measures need to be taken during handling and in particular for transportation.[31] A straightforward lab scale method to synthesize Br_2 in-situ is by bromate-bromine synproportionation under acidic conditions, typically using a $KBrO_3$-KBr mixture and H_2SO_4 as reactants.[32] With the intention of coupling the generated Br_2 as Br_2-feed into the BrCN generator (see Figure 2) the use of the corresponding sodium salts and dilute HBr as acid was more appropriate to ensure homogeneous operation. In order to achieve the appropriate target concentration for the aqueous Br_2 feed (~1 M) streaming into the BrCN generator, an aqueous solution containing $NaBrO_3$ (0.66 M) and NaBr (3.34 M) was mixed with 4 M aqueous HBr at equal flow rates and reacted for 4 min at rt to (theoretically) produce a 1 M Br_2 solution (see Figure 5). For the experimental determination of the Br_2 concentration, Br_2 was extracted into DCM using the Zaiput membrane separator and subsequently used for the bromination of *trans*-stilbene. These experiments confirmed a ≥0.97 M Br_2 concentration (corresponding to ≥97% Br_2 yield).

Figure 5. Set-up of the Br_2 generator. Feed A: 0.66 M aq $NaBrO_3$, 3.34 M aq NaBr, 125 µL min^{-1}; feed B: 4 M aq HBr, 125 µL min^{-1}; PFA coil (0.8 mm i.d.) at rt: 4 min residence time. For more details, see Figure S15. For more details on the bromination of *trans*-stilbene, see Figure S16.

As demonstrated, the Br_2 generator can be applied either as separate module for performing brominations in flow, or, as initially envisaged, be connected as Br_2 feed upstream of the BrCN generator (Figure 1). When operating both generators in series, the BrCN concentration determined via FTIR analysis in fact increased by 10% to 0.8 M (see Figure S17) owing to the higher solubility of Br_2 in water using the in-situ generation concept. After having confirmed that the synthesis of **1a** performed equally well (92% isolated yield) with this set-up (see Figures S18-20), an uninterrupted 4 h run was conducted with a throughput of 2.14 g h^{-1} of **1a**.

In order to process transformations where a reactive crystallization step is essential, e.g. the guanidinylation step toward the synthesis of verubecestat,[28] the reactor set-up was modified. The BrCN stream exiting the coupled Br_2/BrCN generator was introduced into a reaction vessel containing the substrate solution (Figure 6), hence, mimicking a continuous stirred-tank reactor (CSTR) where slurries can be handled. This set-up was then applied for the synthesis of the HBr salt of 2-aminobenzimidazole (**1a**) in DCM. In contrast to the fully continuous operation (vide supra) no co-solvent was used and **1a** therefore precipitated directly from the reaction mixture. Comparable results for the semi-batch and continuous runs were obtained (92% yield).

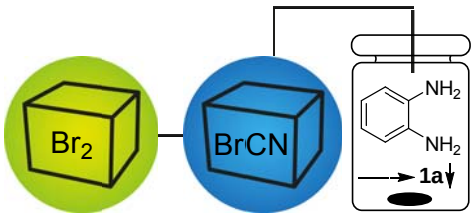


Figure 6. Semi-batch set-up (in-series connected Br_2 and BrCN generators for the synthesis of guanidine HBr salt **1a**. Reaction flask: 1 M solution of *o*-phenylenediamine in DCM; BrCN addition: 0.2 mmol min^{-1} (10 min). For more details, see Figure S21.

In conclusion, two set-ups for the on-demand generation of hazardous BrCN and its subsequent direct utilization have been developed: a fully continuous and a semi-batch format, the latter being preferred for syntheses where a reactive product crystallization step is essential. An integral part of the BrCN generator module is the in-line purification of BrCN via liquid-liquid membrane separation techniques, eliminating the potential exposure risk from traditional distillation[24] and being potentially

more sustainable when production on scale is considered.[33] In addition, a continuous Br_2 generator has also been designed which produces elemental bromine from $NaBrO_3$ and NaBr under acidic conditions. Both generators can be employed independently or coupled in series, as desired. We believe that the in-situ on-demand BrCN generator concept introduced herein will enable chemists from many different fields to now safely use BrCN, a reagent that in recent years has been virtually banned from the arsenal of synthetic chemistry. There probably is a large number of "forbidden" and/or "forgotten" reagents that can be safely generated and used in scalable synthetic operations employing some of the concepts described herein.

Acknowledgements

The CC FLOW project (Austrian Research Promotion Agency FFG No. 862766) is funded through the Austrian COMET Program by the Austrian Federal Ministry of Transport, Innovation and Technology (BMVIT), the Austrian Federal Ministry of Science, Research and Economy (BMWFW) and by the State of Styria (Styrian Funding Agency SFG).

Keywords: chemical generators • continuous flow • cyanogen bromide • bromine • guanidines

[1] a) M. Movsisyan, E. I. P. Delbeke, J. K. E. T. Berton, C. Battilocchio, S. V. Ley, C. V. Stevens, *Chem. Soc. Rev.* **2016**, *45*, 4892-4928; b) B. Gutmann, C. Cantillo, C. O. Kappe, *Angew. Chem. Int. Ed.* **2015**, *54,* 6688-6728*; Angew. Chem.* **2015**, *127,* 6788-6832; c) N. Kockmann, P. Thenée, C. Fleischer-Trebes, G. Laudadioc, T. Noël, *React. Chem. Eng.* **2017**, *2*, 258-280.

[2] P. Poechlauer, S. Braune, B. Dielemans, B. Kaptein, R. Obermueller, M. Thathagar, *Chim. Oggi/Chem. Today* **2012**, *30 (4)*, 51-54.

[3] A. Singh, D.-H. Ko, N. Vishwakarma, S. Jang, K.-I. Min, D.-P. Kim, *Nat. Commun.* **2016**, *7*, 10741.

[4] Cl_2: a) F. J. Strauss, D. Cantillo, J. Guerra, C. O. Kappe, *React. Chem. Eng.* **2016**, *1*, 472-476; b) T. Fukuyama, M. Tokizane, A. Matsui, I. Ryu, *React. Chem. Eng.* **2016**, *1*, 613-615; c) Y. Sharma, S. Moolya, R. A. Joshi, A. A. Kulkarni, *React. Chem. Eng.* **2017**, *2*, 304-308;

[5] a) ClN_3: B. Leforestier, M. Vögtle, *Synlett* **2016**, *27*, 1957-1962; b) BrN_3: D. Cantillo, B. Gutmann, C. O. Kappe, *Org. Biomol. Chem.* **2016**, *14*, 853-857.

[6] CH_2N_2: a) R. M. Maurya, C. P. Park, L. H. Lee, D.-P. Kim, *Angew. Chem. Int. Ed*. **2011**, *50*, 5952-5955; *Angew. Chem.* **2011**, *123*, 6074-6077; b) F. Mastronardi, B. Gutmann, C. O. Kappe, *Org. Lett.* **2013**, *16*, 5590-5593; c) D. Dallinger, V. D. Pinho, B. Gutmann, C. O. Kappe, *J. Org. Chem.* **2016**, *81*, 5814-5823.

[7] a) N_2CHCO_2Et: R. A. Maurya, K.-I. Min, D.-P. Kim, *Green Chem.* **2014**, *16*, 116-120; b) CF_3CHN_2: B. Pieber, C. O. Kappe, *Org. Lett.* **2016**, *18*, 1076-1079; c) CHF_2CHN_2: J. Britton, T. F. Jamison, *Angew. Chem. Int. Ed.* **2017**, *56*, 8823-8827; *Angew.Chem.* **2017**, *129*, 8949-8953;

[8] HN_3: B. Gutmann, J.-P. Roduit, D. Roberge, C. O. Kappe, *Angew. Chem. Int. Ed.* **2010**, 49, 7101-7105; *Angew. Chem.* **2010**, *122*, 7255-7259.

[9] $COCl_2$: S. Fuse, Y. Mifune, T. Takahashi, *Angew. Chem. Int. Ed*. **2014**, *53*, 851-855; *Angew. Chem.* **2014**, *126*, 870-874.

[10] V. Kumar, *Synlett* **2005**, 1638-1639.

[11] J. Morris, L. Kovács, K. Ohe, *e-EROS Encycl. Reagents Org. Synth.* **2015**, 1-12.

[12] D. N. Deaton, A. M. Hassell, R. B. McFadyen, A. B. Miller, L. R. Miller, L. M. Shewchuk, F. X. Tavares, D. H. Willard, L. L. Wright, *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1815-1819.

[13] R. Frei, A. S. Breitbach, H. E. Blackwell, *Angew. Chem. Int. Ed*. **2012**, *51*, 5226-5229; *Angew. Chem.* **2012**, *124*, 5316-5319.

[14] D. Martin, M. Bauer, *Org. Synth.* **1983**, *61*, 35.

[15] a) R. Scholl, F. Kačer, *Ber. Dtsch. Chem. Ges.* **1903**, *36*, 322-331; b) P.-L. Compagnon, B. Grosjean, *Synthesis* **1976**, 448-449; c) K. Okamoto, M. Watanabe, M. Murai, R. Hatano, K. Ohe, *Chem. Commun* **2012**, *48*, 3127-3129.

[16] H. A. Hageman, *Org. React.* **1953**, *7*, 198-262.

[17] A. Machara, M. A. A. Endoma-Arias, I. Císařová, D. P. Cox, T. Hudlicky, *Eur. J. Org. Chem.* **2016**, 1500-1503.

[18] J. von Braun, P. Engelbertz, *Ber. Dtsch. Chem. Ges.* **1923**, *56*, 1573-1577.

[19] E. Gross, B. Witkop, *J. Am. Chem. Soc.* **1961**, *83*, 1510-1511.

[20] M. Murai, R. Hatano, S. Kitabata, K. Ohe, *Chem. Commun.* **2011**, *47*, 2375-2377.

[21] a) https://www.cdc.gov/niosh/ipcsneng/neng0136.html, accessed: 17 August 2017; b) W. E.Luttrell, *J. Chem. Health Safety* **2009**, *16*, 29-30.

[22] BrCN LCLo (lethal concentration low): 92 ppm/10 min inhalation, https://chem.nlm.nih.gov/chemidplus/rn/506-68-3, accessed: 17 August 2017

[23] a) W. W. Hartmann, E. E. Dreger, *Org. Synth.* **1931**, *11*, 30; b) O. Glemsner in *Handbook of Preparative Inorganic Chemistry*, *Vol. 1, 2nd ed* (Ed.: G. Brauer), Academic Press, New York, **1963**, pp. 665-666.

[24] A. Adamo, P. L. Heider, N. Weeranoppanant, K. F. Jensen, *Ind. Eng. Chem. Res.* **2013**, *52*, 10802-10808.

[25] V. Sans, L. Cronin, *Chem. Soc. Rev.* **2016**, *45*, 2032-2043.

[26] J. M. Bell, M. L. Buckley, *J. Am. Chem. Soc.* **1912**, *34*, 14-15.

[27] F. Saczewski, Ł. Balewski, *Expert Opin. Ther. Pat.* **2009**, *19*, 1417-1448.

[28] D. A. Thaisrivongs, S. P. Miller, C. Molinaro, Q. Chen, Z. J. Song, L. Tan, L. Chen, W. Chen, A. Lekhal, S. K. Pulicare, Y. Xu, *Org. Lett.* **2016**, *18*, 5780-5783.

[29] B. P. Charrette, M. A. Boerneke, T. Hermann, *ACS Chem. Biol.* **2016**, *11*, 3263-3267.

[30] T. M. Wróbel, U. Kosikowska, A. A. Kaczor, S. Andrzejczuk, Z. Karczmarzyk, W. Wysocki, Z. Urbańczyk-Lipkowska, M. Morawiak, D. Matosiuk, *Molecules* **2015**, *20*, 14761-14776.

[31] https://www.cdc.gov/niosh/ipcsneng/neng0107.html, accessed: 17 August 2017.

[32] This method is often used in analytical chemistry and $KBrO_3$-KBr mixtures of appropriate stoichiometry are commercially available: D. Diemente, *J. Chem. Educ.* **1991**, *68*, 932.

[33] D. S. Sholl, R. P. Lively, *Nature* **2016**, *532*, 435-437.

10.1002/anie.201708533

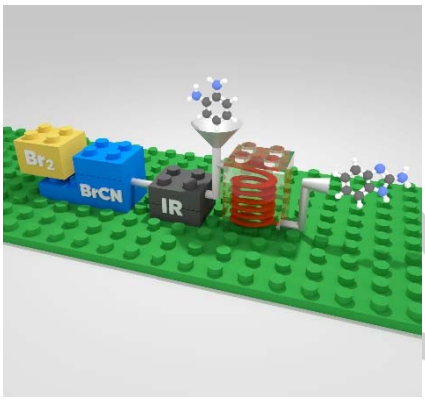
WILEY-VCH

Entry for the Table of Contents (Please choose one layout)

Layout 1:

COMMUNICATION

Cyanogen Bromide on Tap: The highly toxic but synthetically powerful reagent cyanogen bromide (BrCN) has been generated in a fully continuous fashion from benign precursors and directly used for the synthesis of medicinally relevant *N*-heterocycles.



*Gabriel Glotz, René Lebl, Doris Dallinger and C. Oliver Kappe**

Page No. – Page No.

Integration of Bromine and Cyanogen Bromide Generators for the Telescoped Continuous Synthesis of Cyclic Guanidines