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Light-Induced C–H Arylation of (Hetero)arenes by In Situ Generated Diazo Anhydrides

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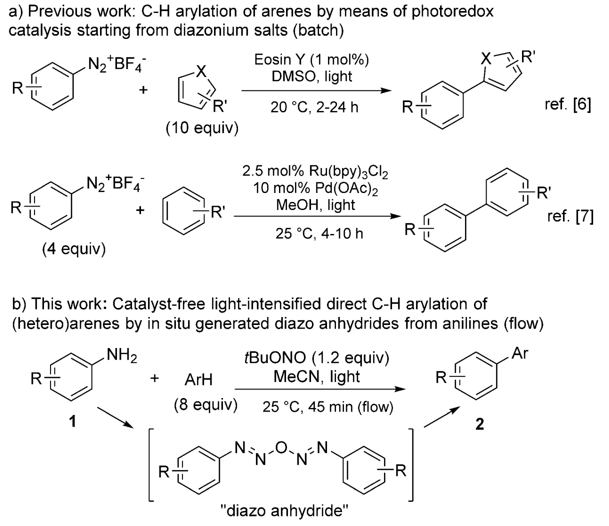
Abstract: Diazo anhydrides (Ar–N=N–O–N=N–Ar) have been known since 1896 but have rarely been used in synthesis. This communication describes the development of a photochemical catalyst-free C–H arylation methodology for the preparation of bi(hetero)aryls by the one-pot reaction of anilines with *tert*-butyl nitrite and (hetero)arenes under neutral conditions. The key step in this procedure is the in situ formation and subsequent photochemical (>300 nm) homolytic cleavage of a transient diazo anhydride intermediate. The generated aryl radical then efficiently reacts with a (hetero)arene to form the desired bi(hetero)aryls producing only nitrogen, water, and *tert*-butanol as byproducts. The scope of the reaction for several substituted anilines and (hetero)arenes was investigated. A continuous-flow protocol increasing selectivity and safety has been developed enabling the experimentally straightforward preparation of a variety of substituted bi(hetero)aryls within 45 min of reaction time.

The synthesis of bi(hetero)aryl moieties arguably is one of the most important transformations in organic chemistry due to the omnipresence of this structural motif in active pharmaceutical ingredients, agrochemicals, and organic materials.[1] The emergence of Pd-catalyzed cross-coupling chemistry in the 1980s has undoubtedly revolutionized bi(hetero)aryl synthesis, broadening the scope and increasing the selectivity and efficiency for the preparation of these types of structures.[2,3] Despite the extraordinary success of cross-coupling chemistry, the search for novel methodologies for the preparation of bi(hetero)aryls continues.[4] These efforts are generally motivated by the ambition to utilize more atom-economic and sustainable starting materials (taking into account both the organometallic species and the aryl halide), and to replace the generally required Pd catalyst/ligand system with less expensive and more abundant catalysts. In this context, the synthesis of bi(hetero)aryl motifs by direct arylation of (hetero)arenes has received significant attention during the past decade owing to the high atom-economy of C–H activation reactions and the broad availability of unfunctionalized aromatic compounds.[5]

Most recently, two elegant light-mediated methods based on the formation of aryl radicals from diazonium salts by means of photoredox catalysis have been described by the groups of König[6] and Sanford.[7] In these protocols, a photoredox catalyst ([Ru(bpy)$_3$Cl$_2$] or Eosin Y) is excited by visible light and subsequently—by single-electron transfer from the excited photocatalyst to the diazonium salt—the corresponding aryl radicals are generated which then react with the arene or heteroarene (Scheme 1a).[8] In view of results described in older literature on aryl radical chemistry associated to the homolytic cleavage of diazo species,[9] it appeared to us that an even simpler C–H arylation route starting directly from anilines avoiding the use of a photoredox catalyst could be conceived. In 1962 Müller and Haiss have described the radical decomposition of dimeric forms of aromatic nitrosamine/diazo hydroxide derivatives,[10] termed diazo anhydrides (Ar–N=N–O–N=N–Ar) when first isolated by Bamberger in 1896.[11] Notably, when the radical fragmentation is performed in aromatic solvents, such as benzene or chlorobenzene, the formation of biaryl products



Scheme 1. Photoredox catalysis and catalyst-free procedures for the C–H arylation of arenes and heteroarenes.

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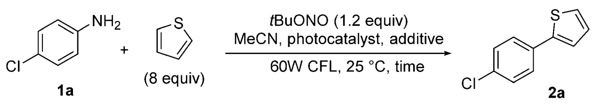
was observed.[10] A related radical decomposition performed under mildly basic conditions had previously been utilized by Gomberg and Bachman for the generation of biaryls from diazonium salts (Gomberg–Bachmann reaction).[12] The proposed mechanism for this transformation also involves a diazo anhydride species,[13] in close analogy to the structures described by Müller and Haiss.[10] The potential of this somewhat underdeveloped diazo anhydride chemistry attracted our attention, as diazo anhydrides have been described as colored species,[11,14] and therefore could likely decompose more efficiently when exposed to light.

Herein we present a light-induced, catalyst-free room temperature C–H arylation methodology for the preparation of bi(hetero)aryls by a one-pot reaction of anilines with *t*BuONO and (hetero)arenes under neutral conditions (Scheme 1b). Anilines are initially transformed to nitrosamines; upon dimerization the corresponding photoactive diazo anhydrides are formed which under irradiation with UV light (>300 nm) decompose to aryl radicals. In the presence of the (hetero)arene the desired bi(hetero)aryls are formed. To further intensify this method and to improve the safety profile, the process has been translated to a continuous-flow procedure providing increased selectivities and a reduction of the overall reaction time to 45 min.

Initially, we performed a set of batch experiments conceived to evaluate the reactivity of in situ generated diazonium salts or nitrosamines (and their corresponding diazo anhydrides) towards C–H arylation of arenes in the presence of light (Table 1). For this purpose, the coupling of 4-chloroaniline (**1a**) with thiophene was selected as a model. Reaction mixtures in which an acid ($BF_3{\cdot}Et_2O$) was added and therefore diazonium tetrafluoroborate salts were present were also evaluated for comparison purposes.[6,7] In the presence of $[Ru(bpy)_3Cl_2]$ (bpy = 2,2′-bipyridyl) excellent conversion was obtained after 3 h irradiation using a 60 W cool-white compact fluorescent lamp (CFL > 360 nm) (Table 1, entry 1). The selectivity, however, was only 63 %, with chlorobenzene being the main side product observed by GCMS analysis (~20 %). Thermal byproducts such as diarylamine and diazo compounds were also observed. When employing Eosin Y as the catalyst, the conversion and selectivity decreased dramatically (entry 2) compared to the ruthenium catalyst. We next evaluated the reactivity using only catalytic amounts of $BF_3{\cdot}Et_2O$. It has been shown that reactions involving the formation of diazonium salts can proceed under these conditions when an acidic proton is released during the catalytic cycle.[15] With 2 mol % of acid (entry 3) 71 % conversion with improved selectivity was observed after 3 h of irradiation. Notably, when the reaction was carried out without a photocatalyst (entry 4) or acid (entry 5) analogous results were obtained. Under these conditions formation of a nitrosamine intermediate instead of a diazonium salt can be expected.[9] In the absence of light significantly lower conversions (17 %) were obtained after 3 h (entry 7). After 24 h in the dark, 83 % of the starting material had been converted although only 58 % of the obtained product corresponded to the desired bi(hetero)aryl (entry 8). The results of these experiments in the absence of light are in agreement with the radical decomposition of diazo anhydrides already observed by Müller and Haiss.[10] However, the data collected in Table 1 clearly demonstrate that light significantly enhances the reaction.

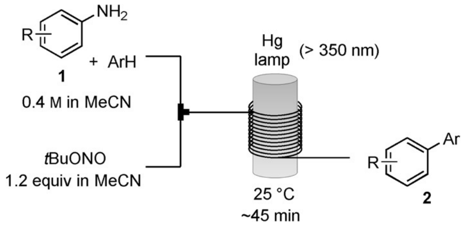
Table 1. Preliminary batch experiments on the reactivity of in situ generated diazonium salts and nitrosamines.[a]



Entry	Additive (equiv)	Photocat. (mol %)	Light Irradiation [h]	Conversion [%][b,c]	Selectivity [%][c]
1	$BF_3{\cdot}Et_2O$ (1)	$[Ru(bpy)_3Cl_2]$ (1)	3	>95	63
2	$BF_3{\cdot}Et_2O$ (1)	Eosin Y (1)	3	24	35
3	$BF_3{\cdot}Et_2O$ (2)	Eosin Y (1)	3	71	70
4	$BF_3{\cdot}Et_2O$ (2)	–	3	69	70
5	–	–	3	74	71
6	–	–	5	81	70
7	–	–	no light, 3 h	17	63
8	–	–	no light, 24 h	83	58

[a] Conditions: **1a** (0.4 mmol), solvent (2 mL), 10 mL Pyrex vial, *t*BuONO (1.2 equiv). [b] Conversion referred to the disappearance of the diazo intermediate that is rapidly formed upon addition of *t*BuONO to the aniline solution. [c] Determined by HPLC and GCMS analysis.

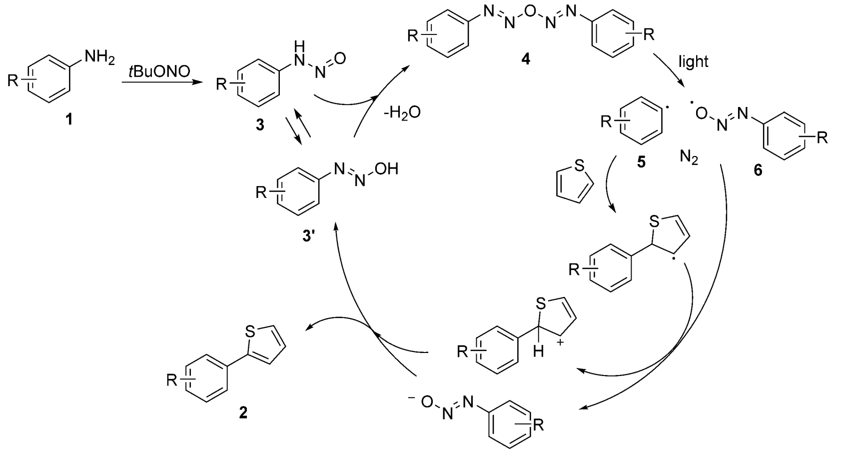
To further intensify this photochemical transformation (Table 1) a continuous-flow process was developed. By using transparent capillary tubing in a microreactor setup very intense irradiation of the reaction mixture can be achieved.[16] The flow setup consisted of two separate feeds, containing a solution of the aniline and the arene in MeCN (feed A) (0.8 mmol scale), and the alkyl nitrite (1.2 equiv) in MeCN (feed B), respectively (Scheme 2). The solutions were pumped to the system and mixed using a standard T-mixer before entering the photoreactor (Vapourtec UV-150 E series), which consisted of transparent fluorinated ethylene propylene (FEP) tubing (1 mm i.d., 10 mL volume) coiled around a power-adjustable medium pressure Hg lamp (max. 150 W). The aniline and nitrite were mixed shortly before entering the photoreactor minimizing potential side reactions outside of the photoreactor (a virtually spontaneous orange coloration of solutions of **1a** after addition of *t*BuONO indicated rapid formation of the diazo intermediate). A UV filter with a 350 nm cutoff was installed in the system providing an emission spectrum analogous to that for the white CFL lamp making batch and flow results comparable (the emission spectra of the filtered Hg lamp and CFL are shown in the Supporting Information). Gratifyingly, under continuous-flow conditions, the reac-



Scheme 2. Continuous-flow setup (schematic).

tion time could be reduced to ~45 min (>99% conversion, compare Table 1, entry 6 for the batch result) and selectivity improved to 85%. Apart from the high irradiation intensity achievable in a capillary tubing in a microreactor, the reaction enhancement is also partially due to the higher efficiency of the medium pressure Hg lamp compared to the household CFL utilized for the batch experiments. The selectivity enhancement is probably due to the fact that the fast photochemical reaction prevents competing thermal processes from occurring.

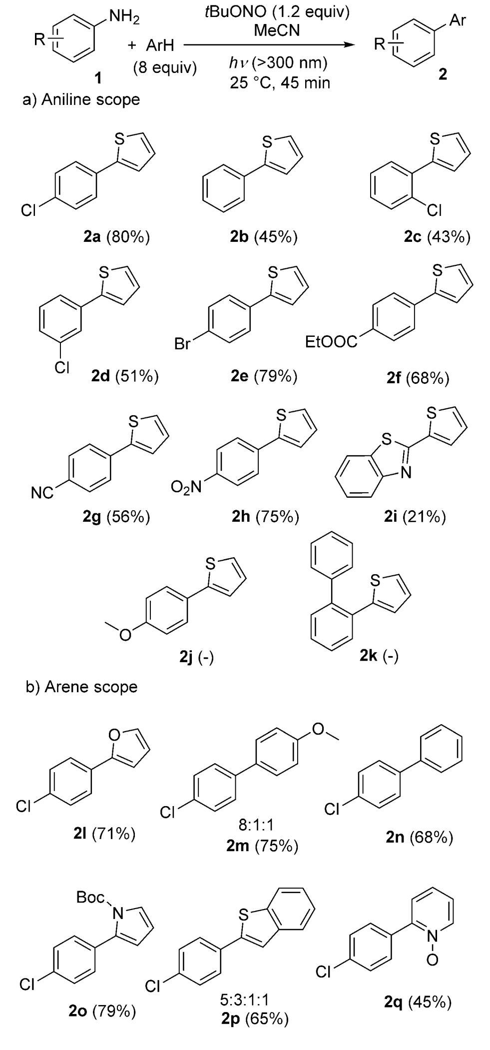
The proposed mechanism for this transformation is based on the formation of diazo anhydrides **4** from the self-condensation of nitrosamine **3**, generated in situ from aniline and alkyl nitrite (Scheme 3). The formation of this type of dimeric (and highly explosive)[11,14] diazo anhydride structure is well established in the literature.[9–11,14] Fragmentation of the diazo anhydride, which can take place spontaneously[10] (thus explaining that the reaction also proceeds in the dark), is accelerated in the presence of light providing the corresponding aryl radical **5**, an azoxy radical **6**, and N_2 gas. Reaction of aryl radical **5** with the (hetero)arene followed by single-electron and proton transfer to **6** results in the desired bi(hetero)aryl, recovering a molecule of nitrosamine (diazo hydroxide **3'**), which can further react (Scheme 3). Although direct evidence for the presence of an unstable diazo anhydride intermediate **4** could not be established, continuous-flow experiments involving variable residence times strongly suggest that the reaction is second-order kinetics with respect to the aniline, thus supporting the formation of a dimeric species (see the Supporting Information for details). DFT calculations on the relative stability of **3**, **3'**, and **4** suggest that these species are in equilibrium (with an energy gap $<2\,\mathrm{kcal\,mol^{-1}}$) and can thus be readily interconverted. Notably, the intermediacy of diazonium salts in the reaction mechanism appears rather unlikely (in contrast to the Gomberg–Bachmann reaction).[12,13] Performing an experiment in which $4\text{-ClC}_6H_4N_2^+BF_4^-$ was prepared independently and used in the photochemical process under identical reaction conditions provided a mixture of products consistent with the formation of an aryl carbocation (see the Supporting Information), in agreement with reports showing that diazonium salts photochemically (350–400 nm) decompose to carbocations instead of radicals.[17]



Scheme 3. Proposed mechanism for the light-induced C–H arylation of arenes with in situ generated nitrosamines.

When unsubstitued aniline (**1b**, R=H) was employed as a substrate instead of 4-chloroaniline (**1a**) poor conversions (35%) were obtained employing identical reaction conditions (see Table S1 in the Supporting Information). Assuming that the mechanism outline in Scheme 3 is correct, we ascribe this significant difference in reactivity to inefficient absorption of light by the diazo anhydride **4** in the case of aniline (R=H). Theoretical calculations (DFT) of the UV/Vis spectra of the diazo anhydrides of aniline and 4-chloroaniline reveal that the λ_{max} in both cases is below 350 nm (335 nm for R=Cl, and 322 nm for R=H). As the lowest wavelength emission peak obtained with the UV filter installed in the photoreactor is at 360 nm, a less than optimal interaction of light with the photochemically active diazo anhydride species **4** can be expected (for details and figure on the theoretical UV/Vis spectra and overlap plots with the lamp emission spectra, see the Supporting Information). We thus decided to fit the UV reactor with a lower wavelength cutoff filter (>300 nm) to enhance irradiation efficiency. Utilizing the new filter conversion for the reaction of aniline (**1b**, R=H) with thiophene dramatically increased. In the case of 4-chloroaniline (**1a**, R=4-Cl), the lamp power could be reduced from 150 to 75 W maintaining excellent conversion and selectivity, providing an 80% isolated yield of 2-(4-chlorophenyl)thiophene **2a** after column chromatography.

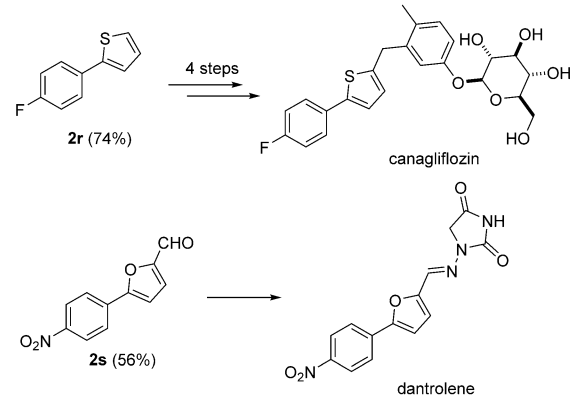
Using the continuous-flow protocol described above a collection of substituted anilines and (hetero)arenes were employed as building blocks for bi(hetero)aryl synthesis (Scheme 4). Thus, 11 different anilines were used as substrates and reacted with thiophene as a model arene (Scheme 4a). Moderate to good isolated product yields were obtained after column chromatography for *ortho*- (**2c**), *meta*- (**2d**), and *para*-substituted (**2e**)



Scheme 4. Reaction scope of anilines and (hetero)arenes under continuous flow conditions. Product **2m** was isolated as an 8:1:1 mixture of the possible isomers and **2p** was isolated as a 5:3:1:1 mixture of isomers. All reactions were carried out on a 0.8 mmol scale. Boc = *tert*-butoxycarbonyl.

haloanilines. The reaction also exhibited compatibility with other functional groups including esters (**2f**), nitriles (**2g**), and nitro groups (**2h**), and also proceeded with 2-aminobenzothiazol (**2i**). As a limitation of this methodology, electron-rich anilines such as anisidine provided poor results (**2j**), leading to formation of polymeric byproducts. In these cases, the aryl radicals **5** (Scheme 3) formed during the process probably react preferentially with the unreacted aniline substrates **1** instead of the (hetero)arene. The presence of a bulky group at the *ortho*-position to the amino group (2-aminobiphenyl) also prevented the reaction from proceeding in high conversion (**2k**). Conversely, several arenes and heteroarenes were tested for the reaction using 4-chloroaniline as the starting material (Scheme 4b). Apart from thiophene used as a model substrate, the reaction proceeded satisfactorily with furan (**2l**) and *N*-Boc-pyrrole (**2o**), as well as with unactivated arenes such as benzene (**2n**) and anisole (**2m**). Reaction with pyridine was unsuccessful and led to the rapid decomposition of the starting materials. However, with pyridine *N*-oxide the reaction worked smoothly, resulting in an orange reaction mixture containing the desired 2-(4-chlorophenyl)pyridine *N*-oxide (**2q**).

The method has further been evaluated for the synthesis of two specific bi(hetero)aryls that are important building blocks in the preparation of active pharmaceutical ingredients (Scheme 5). 2-(4-Fluorophenyl)thiophene (**2r**) is a key intermediate in the synthesis of Canagliflozin, a drug used for the treatment of diabetes.[18] Its bi(hetero)aryl moiety **2r** is typically prepared by cross-coupling chemistry using Pd catalysts, phosphine ligands, and boronic acid starting materials.[18] Using the light-mediated catalyst-free radical protocol developed herein **2r** was prepared in 74% isolated yield using inexpensive 4-fluoroaniline and thiophene as starting materials. Similarly, the reaction of 4-nitroaniline with furfural under the same conditions provided 2-(4-nitrophenyl)furaldehyde (**2s**, 56%), an intermediate in the synthesis of Dantrolene, an important muscle relaxant.[19] Preparation of **2s** is typically carried out by starting from the diazonium salt of 4-nitroaniline in a copper-catalyzed Meerwein arylation.[19] The photochemical continuous-flow method avoids the handling of hazardous diazonium salts and eliminates the use of a metal catalyst. The isolated yields obtained using this protocol are similar to those obtained by König's procedure using Eosin Y as the catalyst in DMSO. Importantly, one of the advantages of working under flow conditions is that the reaction scale (0.8 mmol) can be readily increased by simply operating the reactor for longer periods.



Scheme 5. Application of the light-induced C–H activation method towards the preparation of important bi(hetero)aryl scaffolds.

In summary, this communication has described the development of a light-induced, catalyst-free C–H arylation methodology for the preparation of bi(hetero)aryls from the direct reaction of anilines with arenes and heteroarenes. The anilines are reacted with *t*BuONO and transformed to nitrosamines which, in equilibrium with their corresponding diazo anhydrides, decompose under light irradiation (> 300 nm) at room temperature to aryl radicals. In the presence of (hetero)arenes this radical fragmentation results in the formation of bi(hetero)aryls, producing N_2 gas, H_2O, and *t*BuOH as the only byproducts. In this way hazardous nitrosamine and diazo-type intermediates are generated in situ and are immediately consumed within the reactor avoiding the handling of these substances. In order to make this novel method preparatively useful, a continuous flow protocol was developed enabling overall reaction times of 45 min. We believe that this mild and highly atom-economic procedure has the potential to be developed into a powerful alternative to more traditional methods of bi(hetero)aryls formation.

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Keywords: C–H arylation · continuous-flow chemistry · diazo compounds · photochemistry · radical chemistry

[1] J. Hassan, M. Sévignon, C. Gozzi, E. Schulz, M. Lemaire, *Chem. Rev.* **2002**, *102*, 1359–1469.

[2] C. C. C. Johansson Seechurn, M. O. Kitching, T. J. Colacot, V. Snieckus, *Angew. Chem. Int. Ed.* **2012**, *51*, 5062–5085; *Angew. Chem.* **2012**, *124*, 5150–5174.

[3] a) *Science of Synthesis: Cross Coupling and Heck Type Reactions, Vols. 1–3*, (Eds.: G. A. Molander, J. P Wolf, M. Larhed), Georg Thieme Verlag KG, Stuttgart, **2013**; b) *Metal Catalyzed Cross-Coupling Reactions and More*, (Eds.: A. de Meijere, S. Bräse, M. Oestreich), Wiley-VCH, Weinheim, **2014**.

[4] a) C.-L. Sun, Z.-J. Shi, *Chem. Rev.* **2014**, *114*, 9219–9280; b) I. Hussain, T. Singh, *Adv. Synth. Catal.* **2014**, *356*, 1661–1696.

[5] a) D. Alberico, M. E. Scott, M. Lautens, *Chem. Rev.* **2007**, *107*, 174–238; b) L. Ackermann, R. Vicente, A. R. Kapdi, *Angew. Chem. Int. Ed.* **2009**, *48*, 9792–9826; *Angew. Chem.* **2009**, *121*, 9976–10011; c) G. P. McGlacken, *Organomet. Chem.* **2009**, *35*, 93–129; d) L.-C. Campeau, D. R. Stuart, K. Fagnou, *Aldrichimica Acta* **2007**, *40*, 35–40; e) B.-J. Li, S.-D. Yang, Z.-J. Shi, *Synlett* **2008**, 949–957.

[6] D. P. Hari, P. Schroll, B. König, *J. Am. Chem. Soc.* **2012**, *134*, 2958–2961.

[7] D. Kalyani, K. B. McMurtrey, S. R. Neufeldt, M. S. Sanford, *J. Am. Chem. Soc.* **2011**, *133*, 18566–18569.

[8] An alternative nonphotochemical method in which ascorbic acid has been used as radical initiator has recently been reported: F. P. Crisóstomo, T. Martín, R. Carrillo, *Angew. Chem. Int. Ed.* **2014**, *53*, 2181–2185; *Angew. Chem.* **2014**, *126*, 2213–2217.

[9] For selected reviews, see a) C. Galli, *Chem. Rev.* **1988**, *88*, 765–792; b) N. Zhang, S. R. Samanta, B. M. Rosen, V. Perec, *Chem. Rev.* **2014**, *114*, 5848–5958; c) H. Zollinger, *Angew. Chem. Int. Ed. Engl.* **1978**, *17*, 141–150; *Angew. Chem.* **1978**, *90*, 151–160.

[10] The structure of compounds of the formula Ar_2N_4O has been assigned to either diazo anhydrides (Ar–N=N–O–N=N–Ar) or *N*-nitrosotriazenes (Ar–N(NO)–N=N–Ar), although these species are probably in equilibrium; a) E. Müller, H. Haiss, *Chem. Ber.* **1962**, *95*, 1255–1263; b) E. Müller, H. Haiss, *Chem. Ber.* **1962**, *95*, 570–583; c) see also ref. [14].

[11] E. Bamberger, *Ber. Dtsch. Chem. Ges.* **1896**, *29*, 446–473.

[12] a) M. Gomberg, W. E. Bachmann, *J. Am. Chem. Soc.* **1924**, *46*, 2339–2343; b) for recent literature on the Gomberg–Bachmann reaction, see: G. Pratsch, T. Wallaschkowski, M. R. Heinrich, *Chem. Eur. J.* **2012**, *18*, 11555–11559 and refs cited therein.

[13] C. Rüchardt, E. Merz, *Tetrahedron Lett.* **1964**, *5*, 2431–2436.

[14] T. Kauffmann, H. O. Friestad, H. Henkler, *Liebigs Ann. Chem.* **1960**, *634*, 64–78.

[15] X. Wang, G. D. Cuny, T. Noël, *Angew. Chem. Int. Ed.* **2013**, *52*, 7860–7864.

[16] For recent reviews on continuous flow photochemistry, see: a) Y. Su, N. J. W. Straathof, V. Hessel, T. Noël, *Chem. Eur. J.* **2014**, *20*, 10562–10589; b) J. P. Knowles, L. D. Elliot, K. I. Booker-Milburn, *Beilstein J. Org. Chem.* **2012**, *8*, 2025–2052; c) M. Oelgemoeller, *Chem. Eng. Technol.* **2012**, *35*, 1144–1152.

[17] a) S. M. Gasper, C. Devadoss, G. B. Schuster, *J. Am. Chem. Soc.* **1995**, *117*, 5206–5211; b) P. S. J. Canning, K. McCrudden, H. Maskill, B. Sexton, *Chem. Commun.* **1998**, 1971–1972; c) P. S. J. Canning, H. Maskill, K. McCrudden, B. Sexton, *Bull. Chem. Soc. Jpn.* **2002**, *75*, 789–800; d) J. de Jonge, R. Dijkstra, G. L. Wiggerink, *Recl. Trav. Chim. Pays-Bas* **1952**, *71*, 846–852.

[18] G. Deliencourt-Godefroy, L. Lopes, Preparation of aryl, heteroaryl, *O*-aryl, and *O*-heteroaryl carbasugars and cyclitols as antidiabetic agents, WO 2012160218A1, Nov 29, 2012.

[19] H. R. Snyder, C. S. Davis, R. K. Bickerton, R. P. Halliday, *J. Med. Chem.* **1967**, *10*, 807–810.

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