Radical Reactions

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Iodinated (Perfluoro)alkyl Quinoxalines by Atom Transfer Radical Addition Using *ortho*-Diisocyanoarenes as Radical Acceptors

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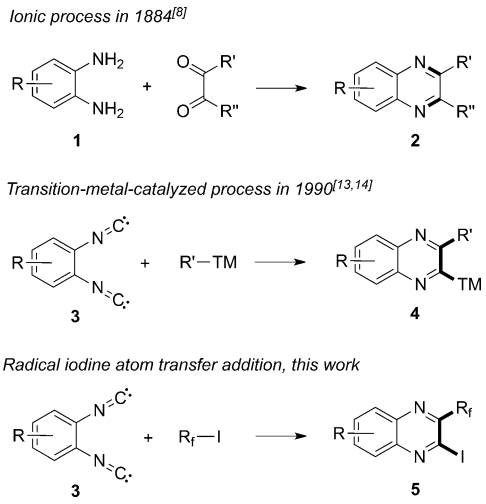
Abstract: *A simple method for the preparation of functionalized quinoxalines is reported. Starting from readily accessible ortho-diisocyanoarenes and (perfluoro)alkyl iodides, the quinoxaline core is constructed during (perfluoro)alkylation by atom transfer radical addition (ATRA), resulting in 2-iodo-3-(perfluoro)alkylquinoxalines. The radical cascades are readily initiated either with visible light or by using α,α′-azobisisobutyronitrile (AIBN). The heteroarene products are obtained in high yields (up to 94%), and the method can be readily scaled up. Useful follow-up chemistry documents the value of the novel radical quinoxaline synthesis.*

The quinoxaline core is an important substructure[1] that can be found in insecticides, fungicides,[2] and herbicides.[3] In addition, quinoxalines show antibacterial,[4] anticancer,[5] and antiplasmodial[6] activity and are also applied as class IIa histone deacetylase (HDAC) inhibitors.[7] Considering the broad application scope of quinoxalines in the medicinal and agrochemical industry, the development of new methods for their preparation is still of great importance.

In the first reported quinoxaline synthesis, the heteroarene core in **2** was constructed in an ionic process through condensation of a 1,2-diketone with *ortho*-phenylene diamine **1** (Scheme 1).[8] Aside from this classical approach, different ionic reactions or copper-catalyzed cyclizations have been developed to access quinoxalines.[1,9,10]

In 1990, Ito and co-workers introduced an elegant approach to the quinoxaline core. They used *ortho*-diisocyanoarenes **3** as substrates that can be readily prepared from the corresponding *ortho*-phenylene diamines.[11,12] Grignard addition to **3** provided quinoxalines in low yields along with a mixture of oligomeric products.[13] Around the same time, it was also shown that **3** can be efficiently polymerized using Pd or Ni catalysis.[14] Addition of an organometallic species R′–TM to **3** generates the metalated quinoxaline **4**, which readily adds to another molecule of **3** in a propagation step. Suginome and co-workers further optimized and used this method for the synthesis of helical polymers.[15] Encouraged by these TM-mediated cascades, we decided to use *ortho*-diisocyanoarenes as radical acceptors and report herein the highly efficient synthesis of 2-iodo-3-(perfluoro)alkylquinoxalines **5** from diisocyanoarenes **3** and (perfluoro)alkyl iodides through atom transfer radical addition[16] (ATRA).



Scheme 1. Construction of the quinoxaline core by ionic, transition-metal-mediated or radical processes. TM = transition metal.

The introduction of perfluoroalkyl substituents into aromatic compounds of pharmaceutical and agrochemical[17] interest is of great value because the perfluoroalkyl group improves their lipophilicity, bioactivity, and metabolic stability.[18] Surprisingly, only a few syntheses of perfluoroalkyl-substituted quinoxalines have been reported. These fluorinated heteroarenes can be accessed by cyclization of *ortho*-phenylene diamines with perfluoroalkylated bis-electrophiles[19] and by quinoxaline post-perfluoroalkylation by copper catalysis[20] or radical addition.[21]

Notably, isonitriles are very good radical acceptors and have been successfully applied to the preparation of phenanthridines, indoles, and other heteroarenes.[22] Along these lines, the groups of Nanni and Curran disclosed a radical cascade for the synthesis of quinoxalines starting from monoisocyanoarenes.[23] Despite intensive investigations, group or atom transfer additions to isonitriles are nearly unexplored. In a rare example, Yamago and Yoshida reported radical PhTe group transfer processes with aryl isocyanides as the acceptors.[24] To the best of our knowledge, radical chemistry on *ortho*-diisocyanoarenes is unknown.

We commenced our studies using *ortho*-diisocyanobenzene (**3a**)[11] and C_4F_9I (10 equiv) as reaction components to give iodoquinoxaline **5ad** (Table 1). Solvent and initiator were varied, and the initial experiments were conducted in acetonitrile (0.1 M) with different azo initiators (8 mol%) at 90 °C for 3 h. V40 (1,1′-azobis(cyclohexanecarbonitrile))

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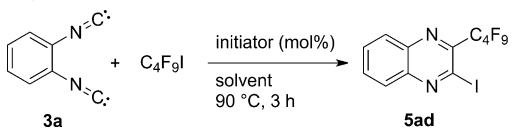
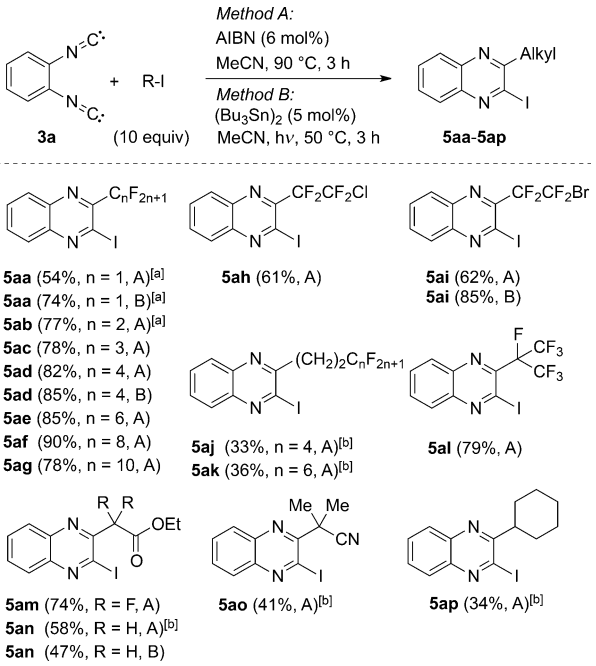
Table 1: Optimization.[a]



Entry	Initiator (mol%)	C_4F_9I [x equiv]	Solvent (M)	Yield [%][b]
1	V40 (8)[c]	10.0	MeCN (0.1)	74
2	AIBN (8)	10.0	MeCN (0.1)	83
3	AIBN (8)	10.0	BTF (0.1)	67
4	AIBN (8)	10.0	EtOAc (0.1)	83
5	AIBN (8)	10.0	DCE (0.1)	83
6	AIBN (4)	10.0	MeCN (0.1)	81
7	**AIBN (6)**	**10.0**	**MeCN (0.1)**	**82 (82)[d]**
8	AIBN (6)	5.0	MeCN (0.1)	76
9	AIBN (6)	7.5	MeCN (0.1)	80
10[e]	***hν***	**10.0**	**MeCN (0.1)**	**85 (90)[d]**

[a] The reactions (0.200 mmol) were carried out under argon. [b] Determined by ^{19}F NMR spectroscopy with BTF as the internal standard. [c] V40: 1,1′-azobis(cyclohexanecarbonitrile). [d] Yield of isolated product, 3 mmol scale. [e] Hexabutylditin (5 mol%) was added, and the reaction was conducted at 50 °C.



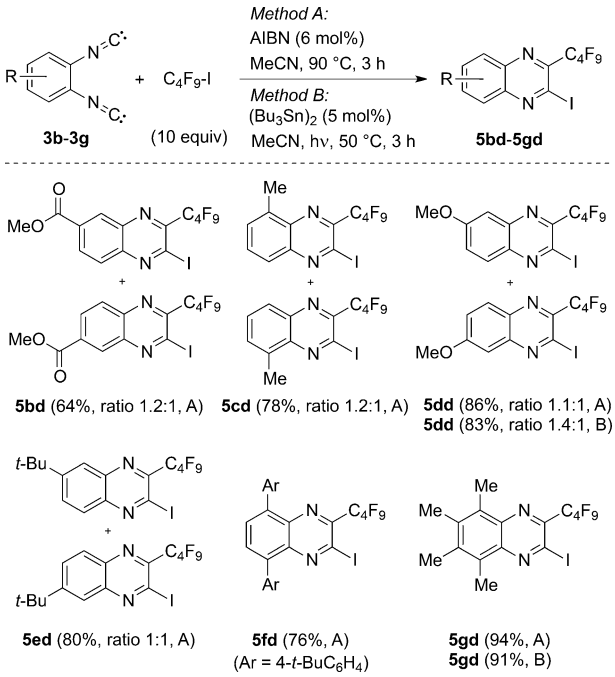
Scheme 2. Substrate scope: Variation of the iodide. [a] Iodide (20 equiv). [b] AIBN (20 mol%).

provided the desired compound **5ad** in 74% yield (Table 1, entry 1). A higher yield was achieved with AIBN (83%, entry 2). Changing the concentration did not lead to a better result (0.07 or 0.2 M, not shown). A solvent screen revealed that the yield was slightly lower in trifluorotoluene (BTF) and the same in ethyl acetate or 1,2-dichloroethane (DCE) compared to the reaction in acetonitrile (entries 3–5). Reducing the amount of AIBN to 6 mol% did not affect the reaction outcome, but with 4 mol%, a slightly reduced yield was noted (entries 6 and 7). With 7.5 or 5.0 equiv of the perfluoroalkyl iodide, the yields slightly decreased to 80% and 76%, respectively (entries 8 and 9). Along with the azo initiators, we also tested initiation by simple irradiation with visible light (400 W) at 50 °C. To avoid inhibition of the radical chain by the molecular iodine formed upon irradiation,[25] hexabutylditin (5 mol%) was added,[26] and product **5ad** was obtained in excellent 85% yield (entry 10). Next, the substrate scope was investigated using the AIBN method at 90 °C (method A; entry 7). In selected cases, the reactions were repeated under irradiation at 50 °C (method B; entry 10). The robustness of both methods was documented by larger-scale syntheses (3 mmol) where methods A and B led to the isolation of **5ad** in 82% and 90% yield, respectively.

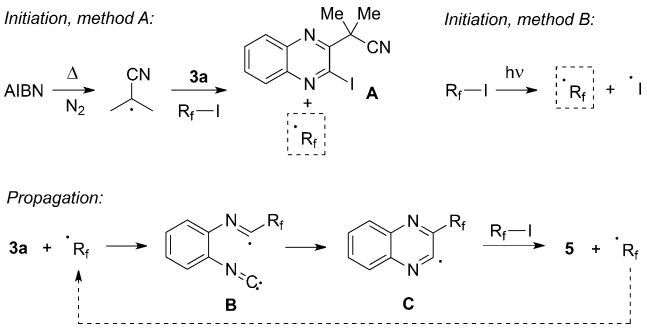
To study the scope of the cascade process with respect to the alkyl iodide, diisocyanobenzene **3a** was reacted with various alkyl iodides under the optimized reaction conditions (methods A and B; Scheme 2). As trifluoromethyl iodide and pentafluoroethyl iodide are gases, they were first condensed at −78 °C and added by syringe. Owing to their high volatility, 20 equiv of the iodide were used in these two cases, and quinoxaline **5aa** and its ethyl congener **5ab** were isolated in 54% and 77% yield, respectively. The reaction with CF_3I was also conducted according to method B, with a yield enhancement to 74%. Upon increasing the length of the perfluoroalkyl chain from C_3 to C_8, the yield improved from 78% to 90% (method A, **5ac**–**5af**). However, for the C_{10} derivative **5ag**, the yield slightly decreased (78%). The reaction with perfluorobutyl iodide was repeated according to method B (**5ad**, 85%). Even with sterically hindered 2-iodoheptafluoropropane, the cascade process worked well, and **5al** was isolated in 79% yield. The selectivity of this reaction regarding the halogen atom transfer step was investigated next. As expected, chlorine and bromine atom transfer are far slower than the iodine atom transfer,[27] and the reactions of $ClCF_2CF_2I$ and $BrCF_2CF_2I$ provided exclusively the iodine atom transfer products **5ah** and **5ai** in 61 and 62% yield. With $BrCF_2CF_2I$, the cascade process was also conducted using method B, and the yield was improved to 85%.

Perfluoroalkylethyl iodides are less reactive, and the corresponding products **5aj** (33%) and **5ak** (36%) were isolated in significantly lower yields. Addition of the perfluoroalkylethyl radicals to the isonitrile is likely to be slower than the corresponding additions with the reactive, pyramidalized perfluoroalkyl radicals.[28] A good result was obtained for the reaction of ethyl iododifluoroacetate with **3a** to give quinoxaline **5am** (74%). As for the alkyl radical series, removing the activating fluorine substituents led to reduced yields also in the ester series, and with ethyl iodoacetate, **5an** was obtained in 58% yield. For this substrate, method B provided a slightly lower yield. The non-fluorinated substrates 2-iodo-2-methylpropionitrile and cyclohexyl iodide provided the corresponding ATRA products **5ao** and **5ap** in moderate yields.

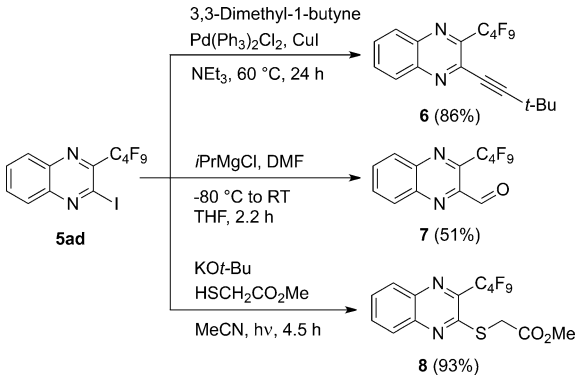
We continued our studies by varying the diisonitrile moiety using C_4F_9I as the alkyl iodide component (Scheme 3). The regioselectivity was low for all tested unsymmetric diisonitriles. Methyl 3,4-diisocyanobenzoate (**3b**) provided the two regioisomers of **5bd** in 64% overall yield with 1.2:1 regioselectivity (method A). Electron-withdrawing substitu-



Scheme 3. Substrate scope: Variation of the isonitrile (regioisomers not assigned).



Scheme 4. Proposed mechanism by ATRA.



Scheme 5. Follow-up chemistry.

ents on the arene do not influence the regioselectivity but seem to reduce the reactivity towards the electrophilic perfluoroalkyl radical as compared to the reaction with **3a**. Indeed, with electron-rich, methoxy-substituted diisonitrile **3d**, the yield increased, and **5dd** was isolated with poor regioselectivity in 86% yield. Method B provided a similar result. Even a bulky *tert*-butyl group could not induce any regioselectivity, and **5ed** was isolated as a 1:1 mixture of regioisomers (80%), and a similar result was obtained for *ortho*-methyl diisonitrile **3c** to give **5cd**. The bulky terphenyl derivative **3f** provided **5fd** in 76% yield, supporting the finding that the steric bulk of substituents on the diisonitrile moiety has only a small influence on the reaction. Tetramethyl substrate **3g** showed the highest reactivity, and **5gd** was isolated in excellent 94% yield (method A). Method B also provided access to this product in high yield.

The suggested mechanism for the cascade process is depicted in Scheme 4. Methods A and B differ only in the initiation step. In the AIBN approach (method A), the azo compound is thermally cleaved to give, after N_2 fragmentation, the 2-cyanopropyl radical, which reacts with diisonitrile **3a** and R_f–I to quinoxaline **A** and the chain-initiating perfluoroalkyl radical R_f. The perfluoroalkyl radical is also accessible by light-induced R_f–I bond homolysis using initiation method B. The thus generated radical R_f then adds to **3a** in a chain reaction to give imidoyl radical **B**, which leads to quinoxalinyl radical **C** through a 6-*endo* cyclization. Iodine atom transfer from R_f–I to aryl radical **C** eventually provides product **5** along with the chain-propagating perfluoroalkyl radical.

To underline the potential of our method, three follow-up reactions were conducted with quinoxaline **5ad** as the substrate (Scheme 5). Sonogashira coupling[29] under standard reaction conditions provided alkynyl quinoxaline **6** in 86% yield. Iodine–magnesium exchange and subsequent formylation with dimethylformamide (DMF) afforded the corresponding aldehyde **7**.[30] Nucleophilic aromatic substitution with methyl thioglycolate gave thioether **8** in 93% yield.

In summary, we have presented a method for the preparation of (perfluoro)alkyl quinoxalines by atom transfer radical addition starting form readily accessible diisonitriles and various inexpensive and commercially available alkyl iodides. Two different modes of initiation, AIBN or light, are reported, which both delivered the targeted heteroarenes in high yields (up to 94%). Notably, the reactions can be easily scaled up, and the iodoquinoxalines obtained in these cascades are valuable substrates for follow-up chemistry.

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Keywords: (perfluoro)alkylation · atom transfer · cascade reactions · quinoxalines · radical addition

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