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Photochemical Arylation of Brønsted Acids with 2-Azidobenzimidazole

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Irradiation of *N*-benzylated 2-azidobenzimidazoles at 300 nm in the presence of an excess amount of carboxylic acids results in a novel regioselective synthesis of 2-amino-6-oxybenzimidazoles in isolated yields of 60–70 %. It is also possible to regioselectively introduce 6-bromo, 6-chloro, and 6-triflyloxy groups. Irradiation in dichloromethane in the absence of external nucleophiles revealed that after loss of nitrogen, the benzimidazolylnitrene probably undergoes coarctate ring opening to an *N*-cyano diaza-*o*-xylylene intermediate.

Introduction

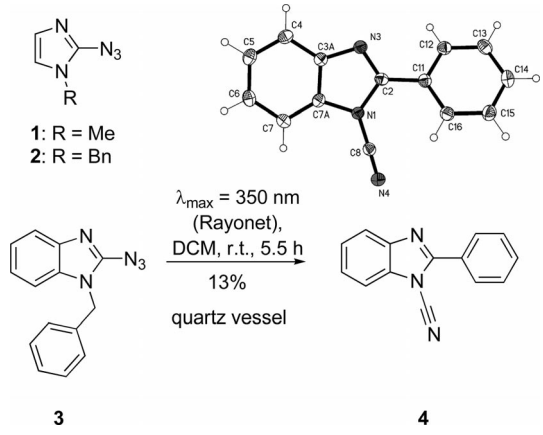
Photochemical conversions are of general interest for chemical biology, because they are orthogonal to most biochemical processes. In this communication we report on a new possibility to arylate carboxylic and other Brønsted acids under photochemical conditions starting from 2-azidobenzimidazole. The arylation is regioselective and proceeds in good yields.

It is known that five-membered heterocycles with an azido group in the *ortho*-position to one of the heteroatoms undergo ring opening under thermal or photochemical conditions.[1] The reaction commences with loss of dinitrogen and formation of the nitrene, followed by cleavage of the bond between the ring heteroatom and the nitrene-substituted atom. In a seminal publication, such opening reactions have been classified by Herges as proceeding via coarctate transition states.[2] The resulting formal ene-ene-nitriles have cyclized further to interesting heterocycles, for example, in the case of the high-yielding conversion of *N*-amino-2-azido-1,3,4-triazoles into 3-amino-1,2,4,5-tetrazines,[3] the reaction of 1-amino-2-azidoimidazoles into a mixture of 1,2,3-triazoles and 3-amino-1,2,4-triazines,[4] or the irradiation of 3-azidopyrazole-4-carbaldehydes into a mixture of 4-cyanopyrazoles and 4-cyano-3-azofurans.[5]

Results and Discussion

We decided to investigate 2-azidoimidazoles, because they can be obtained in a facile manner through azidation of 2-lithiated imidazole derivatives, as applied to the synthesis of several pyrrole-imidazole alkaloids.[6] As initial candidates, we irradiated 2-azido-1-methylimidazole (**1**) and 2-azido-1-benzylimidazole (**2**) in EtOH or water in a Rayonet photoreactor (RPR 3000/3500 lamps with emission maxima at 300 and 350 nm, respectively, quartz reaction vessel). However, after evolution of nitrogen, intractable product mixtures were obtained.

The ^{1}H NMR spectra of the crude product mixtures obtained from **1** indicated loss of the olefinic imidazole CH signals. This prompted us to protect the olefinic double bond of imidazole by annulation of a benzene ring and to investigate the corresponding benzimidazoles. When 2-azido-1-methylbenzimidazole was irradiated in MeOH or DCM (λ_{max} = 300 nm) the orange-colored 1,2-bis(1-methylbenzimidazol-2-yl)diazene was isolated in very low yield (3 %). The picture did not change in 10-fold higher dilution (0.015 M). A little more promising was the behavior of 2-azido-1-benzylbenzimidazole (**3**) upon irradiation (λ_{max} =



Scheme 1. 2-Azidoimidazoles employed in initial irradiation experiments.

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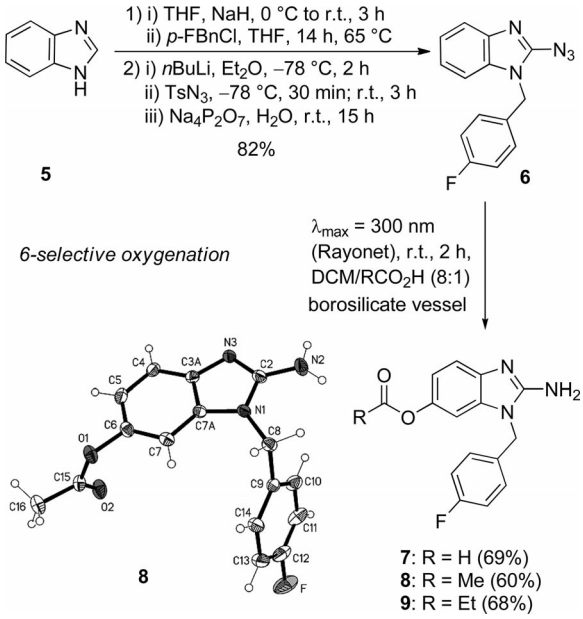
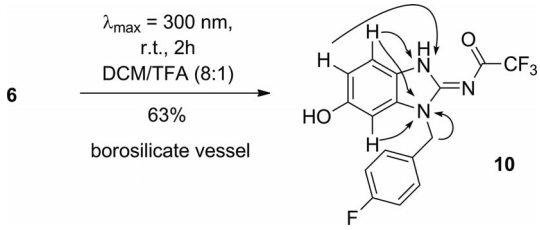
350 nm) in DCM (0.01 M, Scheme 1). The major product (13% isolated yield) was 2-phenylbenzimidazol-1-carbonitrile (**4**), as proven by X-ray analysis.

To enable facile judgment by ^{19}F NMR spectroscopy before workup, the benzyl group was replaced by a *p*-fluorobenzyl group. The synthesis of fluorinated azidobenzimidazole **6** required *N*-benzylation of benzimidazole (**5**), followed by 2-azidation after lithiation and quenching with tosylazide (53%).[7] We optimized the azidation by changing the solvent from THF to Et_2O and by workup employing $Na_4P_2O_7$ (Scheme 2).[8] Azide **6** can be stored in the dark at room temperature for several months without decomposition.



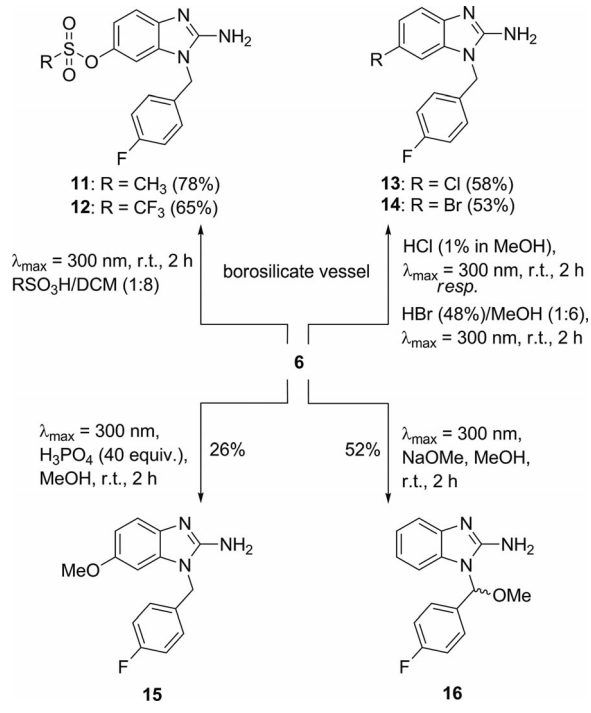
Scheme 2. Regioselective 6-oxygenation of fluorinated 2-azidobenzimidazole **6** by irradiation in the presence of carboxylic acids.

Irradiations (λ_{max} = 300 nm) of **6** were carried out by employing potential reaction partners (e.g., acetic acid, benzaldehyde, furan, diethylamine) as cosolvents in DCM. We replaced the quartz by a borosilicate vessel, which cut the short-wavelength section of the emission spectrum off below 295 nm and diminished the number of byproducts in some cases. The ^{19}F NMR spectra of the crude product mixtures revealed that very selective reactions occurred with carboxylic acids (Scheme 2), whereas less acidic reaction partners led to complex mixtures. Irradiation of azide **6** in AcOH/DCM (1:8) gave product **8** (confirmed by X-ray analysis) in 60% yield and in pure AcOH the yield was 92%. In the case of trifluoroacetic acid, transfer of the trifluoroacetyl group from the oxygen to the amino nitrogen took place during aqueous workup, resulting in overall 6-hydroxylation (Scheme 3). In a quartz tube, the yield of 63% (for **10**) was diminished to 28%. The structure of product **10** was secured by ^1H–^{15}N HSQC and HMBC experiments with the decisive correlation observed between 5-H (δ = 6.77 ppm) and protonated N-3 (δ = –247.6 ppm, [D_6]-DMSO).



Scheme 3. 6-Hydroxylation of 2-azidobenzimidazole with simultaneous protection of the terminal amino group. ^1H–^{15}N HMBC correlations are shown.

Sulfonic acids were also suitable. The synthesis of 2-amino-6-sulfonyloxybenzimidazole **11** was possible in MeSO_3H/DCM (1:8) in high yield (78%, Scheme 4). Of particular interest with respect to subsequent C–C coupling reactions will be the incorporation of CF_3SO_3H, which provided aryl triflate **12** (65%). It was also possible to obtain 6-chlorinated and 6-brominated benzimidazoles **13** and **14**, respectively, in acceptable yields (50–60%) by employing the corresponding mineral acids (Scheme 4). Chlorinated compound **13** was also formed in the presence of NH_4Cl, which shows that ammonia is not incorporated.

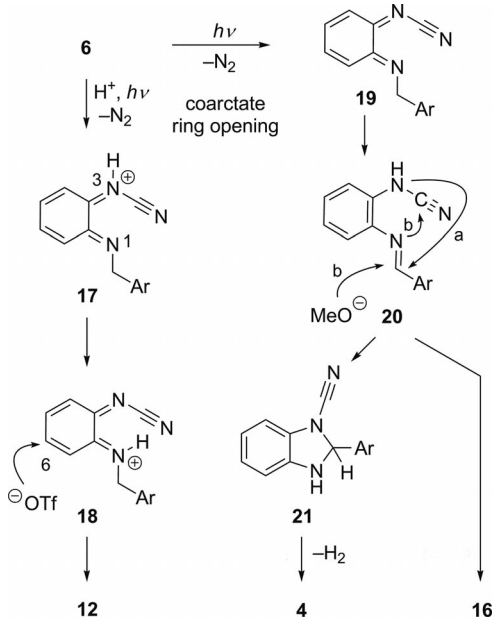


Scheme 4. Regioselective sulfonylations, halogenations, and methoxylations of 2-azidobenzimidazole **6**.

Differing from carboxylic and sulfonic acids, alcohols were not incorporated into the 6-position when used as the only cosolvent of DCM. However, 6-methoxylation was achieved by applying a mixture of MeOH and phosphoric acid (Scheme 4), indicating the participation of protonated intermediates. Interestingly, the benzylic methylene group was methoxylated in 52% yield on irradiation of **6** in Na-

OMe/MeOH. This makes it likely that the benzylic carbon becomes part of an imine moiety under deprotonating conditions.

Scheme 5 outlines possible reaction mechanisms. On irradiation, azide **6** loses dinitrogen to afford the corresponding nitrene. In the presence of Brønsted acids, the protonated form of that nitrene predominates and cleavage of N1–C2 via a coarctate transition state affords protonated *N*-cyanodiazaxylylene **17**. McClelland and co-workers proposed a similar ring opening for the nitrene derived from 2-azido-1-methylimidazole in aqueous solution.[9] Pozharskii and co-workers have shown that oxidation of 1,2-diaminobenzimidazole leads to the corresponding coarctate ring opening after oxidation, affording 3-amino-1,2,4-triazines through re-cyclization.[10] Proton shift at **17** to the more basic nitrogen affords intermediate **18**. Nucleophilic attack occurs at C6, which is the β-position of an α,β-unsaturated iminium moiety. Ring closure to the benzimidazole would be followed by proton transfer from C6 to the exocyclic nitrogen to afford, for instance, aryl triflate **12**.



Scheme 5. Possible reaction mechanisms under protonating and non-protonating conditions via coarctate ring opening (Ar = *p*-fluorophenyl).

Ring cleavage of an intermediate nitrene is also in agreement with the products obtained in the absence of Brønsted acids. Although isolated in a yield of only 13%, structure **4** proves that cleavage of the imidazole section can occur. In the absence of a nucleophile, intramolecular attack by the cyanamide nitrogen becomes the main pathway (Scheme 5). After [1,5] hydrogen shift to aromatic intermediate **20**, cyclization would afford imidazoline **21**, which has to undergo oxidation to product **4**. Compound **4** has been obtained by Wentrup and co-workers by a different pathway as the main product starting from 5-phenyltetrazolo[1,5-*c*]quinazoline or 4-phenyltetrazolo[1,5-*a*]quinoxaline (59 or 88%).[11]

In the presence of methoxide, imine **20** is intercepted by attack at the most electropositive imine carbon, followed by cyclization to methoxylated product **16**.

Conclusions

In summary, we have discovered a new efficient method for the synthesis of 6-oxygenated and -halogenated aminobenzimidazoles, which may become of preparative use in medicinal chemistry. Currently, 2-aminobenzimidazoles are assembled from suitably substituted *o*-phenylendiamines with the amino group introduced by either nucleophilic attack at 2-chlorobenzimidazole[12] or condensation with urea derivatives.[13] An important application of our reaction may become the use of 2-azidobenzimidazoles for photolabeling of carboxylic acids, as they occur in proteins as side chains of aspartic and glutamic acid. We are currently investigating that option.

Experimental Section

General Procedure for the Irradiation of 6 in the Presence of Carboxylic or Sulfonic Acids: A solution of **6** (50.0 mg, 0.187 mmol) and a carboxylic acid or sulfonic acid (2 mL) in DCM (16 mL) was irradiated for 2 h at λ_{max} = 300 nm (borosilicate glass, Rayonet RPR-200 reactor, equipped with eight RPR-3000 Å lamps, 35 °C). Saturated aqueous $NaHCO_3$ was added, until pH 8–9 was reached. The organic phase was separated, and the aqueous phase was extracted with EtOAc (3×). The combined organic phases were dried with $MgSO_4$, filtered, and concentrated. The crude residue was purified by column chromatography on silica. For further experimental procedures and data, see the Supporting Information.

CCDC-858062 (for **4**) and -858063 (for **8**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Supporting Information (see footnote on the first page of this article): Experimental procedures, spectroscopic and analytic data, and copies of the NMR spectra for all new compounds.

Acknowledgments

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