Cycloadditions

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The Trapping of Phenyldiazenes in Cycloaddition Reactions**

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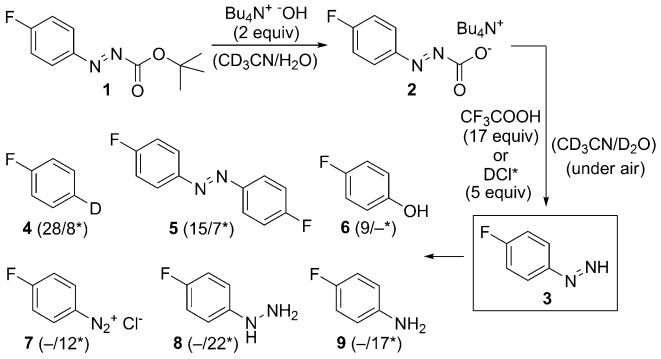
Abstract: *The reactivity of phenyldiazenes was studied intensively in the late 1960s, but not much is known about their behavior under acidic conditions. Based on the formation of phenyldiazenes from phenylazocarboxylates, we herein describe how reactions of phenyldiazenes can be directed into ionic or radical pathways. Cycloaddition reactions with furans leading to pyridazinium salts represent the first examples for the direct trapping of phenyldiazenes with conservation of the N=N moiety.*

The occurrence of aryldiazenes (aryldiimides, ArN=NH) as intermediates was first proposed by Widman[1a] in 1895 based on his investigations on the acid-induced decomposition of arylazocarboxylate potassium salts (ArN=NCOOK) to the corresponding arenes (ArH). About one decade later, Chattaway[1b] evoked phenyldiazene to rationalize the formation of benzene and nitrogen from the oxidation of phenylhydrazine. Generally, the synthetic approaches to diazenes, which were significantly broadened starting in the mid-1960s,[2] can be divided into four subgroups including fragmentations, eliminations, oxidations, and reductions.[3] At that time, Kosower[4] achieved the observation of phenyldiazenes by photometry and found that these intermediates have a much prolonged lifetime in diluted solutions as well as in the absence of oxygen. Moreover, phenyldiazene was shown to be less stable under acidic than under neutral conditions, but the reaction course in the presence of acids such as perchloric acid remained "obscure".[4e] Strongly basic conditions, on the other hand, lead to the decomposition of aryldiazenes via aryldiazenyl ($ArN{=}N^-$)[5] and aryl anions,[6] which can be used to generate arynes.[7] Reactions of diazenes with conservation of the N=N moiety have so far only been achieved for alkyl derivatives through base-mediated additions to aldehydes.[8] Alternatively, diazenes can be stabilized through the formation of metal complexes.[9] Such complexes have gained remarkable importance in the field of biochemistry,[10] and have been investigated as model intermediates for the chemical fixation of nitrogen.[11]

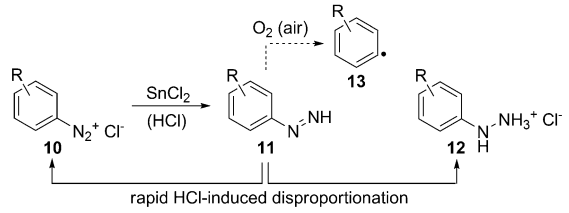
Our interest in the "obscure" behavior of phenyldiazenes[12,13] under acidic conditions arose from two experiments in which to the phenylazocarboxylate salt **2**[12c]—conveniently accessible from azoester **1**—was added at once solutions of either hydrochloric or trifluoroacetic acid to give phenyldiazene **3** as a reactive intermediate upon decarboxylation (Scheme 1).[4d] An analysis of the resulting product mixtures by ^{1}H NMR spectroscopy revealed strong differences in the reaction course.



Scheme 1. Behavior of phenyldiazenes in the presence of trifluoroacetic or hydrochloric acid.

Trifluoroacetic acid largely directs the subsequent reactions of diazene **3** into radical pathways, as is apparent from the predominant formation of the deuterium-abstraction product 4-deuterofluorobenzene (**4**), azobenzene **5** (by addition of the aryl radical to **2** or **3**), and 4-fluorophenol (**6**).[14,15] Hydrochloric acid, on the other hand, leads to diazonium salt **7** and hydrazine **8**—most probably by redox disproportionation of diazene **3**.[16] Under the strongly acidic conditions hydrazine **8** can even be further reduced to aniline **9**.[17]

The disproportionation of diazene **3** under strongly acidic conditions provides a good explanation for the feasibility of reductions of aryl diazonium salts **10** to hydrazines **12** (Scheme 2).[18] Such reactions are very likely to proceed via diazenes **11** and usually good results can be obtained by slow addition of tin(II) chloride in hydrochloric acid to **10**, even though the transformations are typically conducted under air



Scheme 2. Tin(II)-mediated reduction of diazonium salts in hydrochloric acid.

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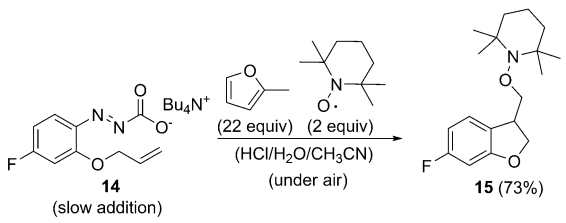
atmosphere.[19] Given that a very rapid acid-induced disproportionation of diazene **11** to **10** and **12** does occur, the formation of **12** in high yield becomes comprehensible, since diazene **11** does not react with oxygen to give radical **13**. Astonishingly, this mechanistic detail of tin(II)-mediated reductions of diazonium salts appears not to have been described in literature before.

To further explore the reactivity of phenyldiazenes, we first focused on the selective generation of aryl radicals.[12c] For this purpose, the experiment with hydrochloric acid presented in Scheme 1 was repeated with the modification that the azocarboxylate salt was added slowly to the acidic reaction mixture, which now also contained a suitable radical scavenger. If azobenzene **5** and products **7**–**9** really resulted from bimolecular reactions involving two phenyldiazenes **3**, or an aryl radical and a diazene, these compounds should now be formed in significantly lower yields.

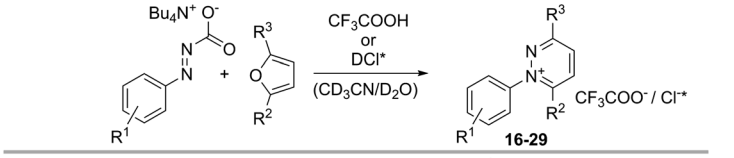
As proven in several experiments, these modified conditions do indeed lead to Sandmeyer and Meerwein reaction products with high selectivity (see the Supporting Information). A selected transformation from this series with azocarboxylate **14**, 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO), and 2-methylfuran was set up to get an insight into the lifetime of the intermediate diazene (Scheme 3). Since no side reaction with 2-methylfuran occurred (as will be shown below to be possible) and only dihydrobenzofuran **15**[20,21] was observed as a product, the diazene resulting from **14** appears to be rapidly transformed into the corresponding aryl radical by reaction with oxygen or TEMPO.[22]



Scheme 3. Selective generation of aryl radicals through slow addition of azocarboxylate **14** under air atmosphere.

The more challenging task now was to selectively direct aryldiazenes into other reactions that do not proceed via radicals. For this purpose, we turned our attention to hetero-Diels–Alder cycloadditions,[23] which have so far been described almost exclusively for azodicarboxylates featuring a comparably electron-poor N=N moiety.[24,25] To increase the lifetime of the phenyldiazenes, we limited the exposure of the reaction mixture to air by conducting the following transformations in NMR tubes. Trifluoroacetic acid was employed since it readily generates diazenes from azocarboxylates, but does not lead to disproportionation (Scheme 1). Table 1 summarizes the results of this study.

Table 1: Synthesis of pyridazinium salts **16**–**29** through cycloaddition reactions of phenyldiazenes to furans: scope and limitations.[a,b]



(1)
16: R^1 = 4-F (10%)
17: R^1 = 4-NO_2 (39%)

(2)
18: R^1 = 4-F (76%, 63%*)
19: R^1 = 2-allyloxy, 4-F (93%, 82%*)
20: R^1 = 4-OMe (44%)
21: R^1 = 4-NO_2 (72%)

(3)
22: R^1 = 4-F (*quant*)
23: R^1 = 3,4,5-F_3 (*quant*)
24: R^1 = 4-Br (*quant*)
25: R^1 = 2-allyloxy, 4-F (*quant*)
26: R^1 = 4-OMe (*quant*)
27: R^1 = 4-NO_2 (99%)

(4)
28: R^4 = H (64%)
29: R^4 = Cl (54%)

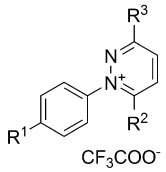
[a] See the Supporting Information for reaction conditions. [b] Yields determined with dimethyl terephthalate as an internal standard. Products further analyzed and isolated by HPLC.

Only low to moderate yields of pyridazinium salts **16** and **17** were obtained in the experiments with unsubstituted furan (group 1),[26] thereby indicating a strong preference for an electron-withdrawing substituent on the aromatic core of the azocarboxylate. The product yields significantly increased when 2-methylfuran was used as diene and only one regioisomer was found for the pyridazinium salts **18**–**21** (group 2). Comparative experiments within this group showed that cycloadditions leading to **18** or **19** can also be achieved with hydrochloric acid, but with the expected disproportionation occurring as a side reaction, as evidenced by the formation of phenylhydrazines in small amounts (Scheme 1). All attempts to use acetic instead of trifluoroacetic acid were unsuccessful since the decarboxylation of the azocarboxylate then proceeded slowly and oxidation of the newly formed diazene by the remaining azocarboxylate fully directed the reaction towards radical products.

Even higher yields than those with 2-methylfuran could be obtained with 2,5-dimethylfuran (group 3, **22**–**27**), and dependence on the ring substituents was no longer observed anymore. A phenyl group in the 2-position of the furan was also tolerated and complete regioselectivity was maintained; however the yields were remarkably decreased (group 4, **28** and **29**), which is in agreement with the assumption that the furans act as electron-rich dienes. The synthetic applicability was demonstrated in four reactions conducted on a 1 mmol scale (Table 2).

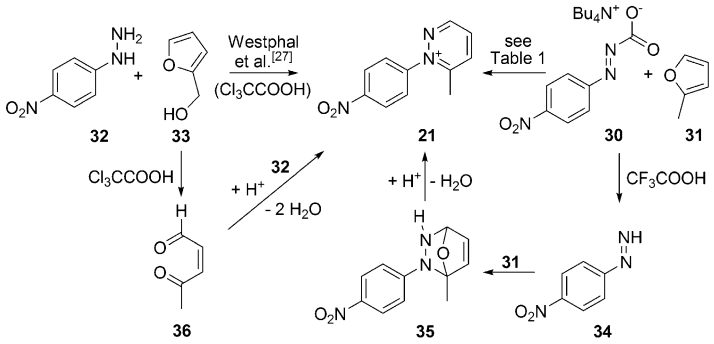
To unambiguously determine the regioselectivity of the cycloaddition reaction and the structure of the pyridazinium salts, compound **21**, obtained from phenylazocarboxylate **30** and 2-methylfuran (**31**) (Table 1 and Scheme 4, right), was compared with a sample of **21** prepared according to a procedure described by Westphal and Himmelspach (Scheme 4, left)[27] which started from 4-nitrophenylhydrazine (**32**) and furfuryl alcohol (**33**).[28,29] Notably, the oxidation

Table 2: Synthesis of pyridazinium salts: preparative experiments.



Entry	Pyridazinium trifluoroacetate[a]	Yield[b]
1	**18**: $R^1 = F$, $R^2 = CH_3$, $R^3 = H$	96
2	**21**: $R^1 = NO_2$, $R^2 = CH_3$, $R^3 = H$	74
3	**22**: $R^1 = F$, $R^2 = R^3 = CH_3$	95
4	**27**: $R^1 = NO_2$, $R^2 = R^3 = CH_3$	95

[a] See Experimental Section for reaction conditions. [b] Yields determined after purifcation by column chromatography.



Scheme 4. Pyridazinium synthesis by condensation (left) and proposed mechanism for the cycloaddition (right).

states of the reactant pairs **31**/**34** and **32**/**36** here are complementary.

First support for the proposed cycloaddition mechanism via the bicyclic intermediate **35** came from the observation that pyridazinium salt **21** was formed along with its regioisomer **21′** under the conditions of Westphal (Figure 1, top).[27a] This excludes a pathway in which diazene **34** initially oxidizes 2-methylfuran (**31**) to give ketoaldehyde **36** and hydrazine **32** as reactants for the known condensation (Scheme 4, left).

To verify that phenyldiazenes do indeed occur as intermediates in our reactions, UV spectra were recorded immediately after the addition of trifluoroacetic acid to the phenylazocarboxylate. The spectra obtained for 4-nitrophenyldiazene (**34**) and 4-bromophenyldiazene were in perfect agreement with those reported by Kosower[5b] (see the Supporting Information). This was also true for the UV spectra recorded after treatment of the solutions containing **34** and 4-bromophenyldiazene with air, which led to their immediate decomposition.

With respect to the extremely high reactivity of phenyldiazenes towards oxygen, the cycloaddition with furans must also be a very rapid process. This becomes evident from the absence of any radical cyclization product comparable to dihydrobenzofuran **15** (Scheme 3) in the reactions yielding pyridazinium salts **19** and **25** (Table 1), although the reaction mixtures were not degassed. The conditions applied for the cycloadditions even turned out to be useful to trap phenyldiazene as an intermediate in the tin(II)-mediated reduction of 4-fluorophenyldiazonium chloride under air atmosphere (cf. Scheme 2).[30]

To further support the proposed mechanism, experiments were conducted to exclude three other reactive intermediates (see the Supporting Information). Under conditions comparable to those used for the cycloadditions (Table 1), *tert*-butyl azocarboxylate **1** and 2-methylfuran (**31**) did not undergo any reaction. This also eliminates the participation of the corresponding free acid before decarboxylation, since the reactivity of the ester **1** and the acid at the N–N double bond can be expected to be similar. 4-Fluorophenyldiazonium tetrafluoroborate, when reacted with 2-methylfuran (**31**), only gave low yields of a dihydropyridazinone and a pyrrolone,[31] and can therefore also be excluded as a central intermediate.

The proposed cycloaddition pathway could be further confirmed by a preliminary experiment with cyclopentadiene (**37**) and azocarboxylate salt **30**, which gave unstable diazabicycloheptene **38** (Scheme 5).[32]

Finally, a comparison of the cycloaddition to phenyldiazenes with similar reactions of nitrosobenzenes[33,34] revealed an interesting difference in regioselectivity (Scheme 6). Whereas the carbon atom with the largest HOMO coefficient in diene **39** is known to selectively attack the nitrogen atom of nitrosobenzene (**40**; Scheme 6, top),[35] the corresponding site of 2-methylfuran (**31**), which is at the 5-position,[36] forms a new bond to the terminal nitrogen atom of phenyldiazene **3** (Scheme 6, bottom). Whether the acids that

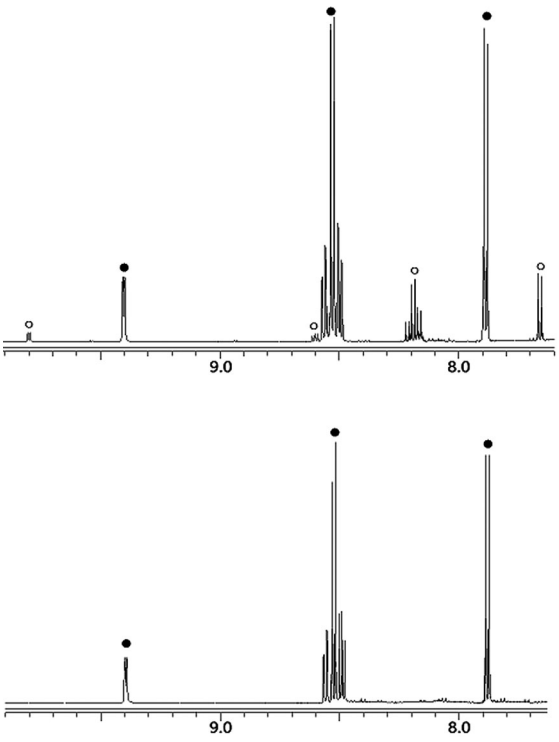
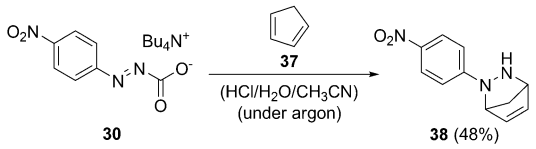
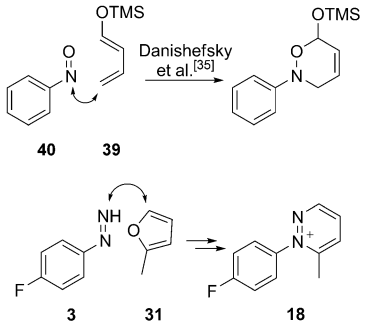


Figure 1. ^{1}H NMR spectra of **21** (●) prepared according to Westphal and Himmelspach[27a] (top, with regioisomer **21′** ○) and as obtained from the cycloaddition reaction (bottom).



Scheme 5. Extension to cyclopentadiene.



Scheme 6. Regioselectivity in cycloadditions of nitrosobenzenes[35] and phenyldiazenes.

are necessary to generate phenyldiazenes from phenylazocarboxylate anions do have some additional activating or directing effect on either the diazene or the furan can currently not be excluded.[37,38]

In summary, we have shown that phenyldiazenes are more valuable synthetic intermediates than previously thought. Radical reactions, which were the main destiny of diazenes so far, can be selectively achieved in the presence of air and through the slow addition of the azocarboxylate precursor to the acidic reaction mixture. At higher concentrations of the diazene, strong acids such as hydrochloric acid enable redox disproportionations. Cycloadditions to furans can be achieved with phenyldiazenes generated from azocarboxylate salts by either hydrochloric or trifluoroacetic acid. These studies provide the first examples for the trapping of phenyldiazenes with conservation of the N=N moiety, a new straightforward and efficient access to pyridazinium salts,[27,39] and a rationale for the high yields attainable in tin(II)-mediated reductions of diazonium salts. Further investigations on the applicability of other dienes as well as on the effects governing regioselectivity are currently underway in our laboratory.

Experimental Section

General procedure for the preparation of pyridazinium trifluoroacetates (Table 2): Under argon atmosphere tetrabutylammonium hydroxide (1.5 M in H_2O, 2.00 mmol, 1.33 mL) was added to a solution of the *tert*-butyl phenylazocarboxylate (1.00 mmol) in CH_3CN (4–8 mL). The appropriate furan (4.0 mmol) and afterwards trifluoroacetic acid (8.6 mmol, 0.66 mL) were added to this mixture. The reaction mixture was stirred for an additional 10 min and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (CH_2Cl_2/MeOH/CH_3COOH = 4:1:0.05). The pyridazinium trifluoroacetate was obtained after evaporation with an excess of trifluoroacetic acid and drying in vacuo.

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