

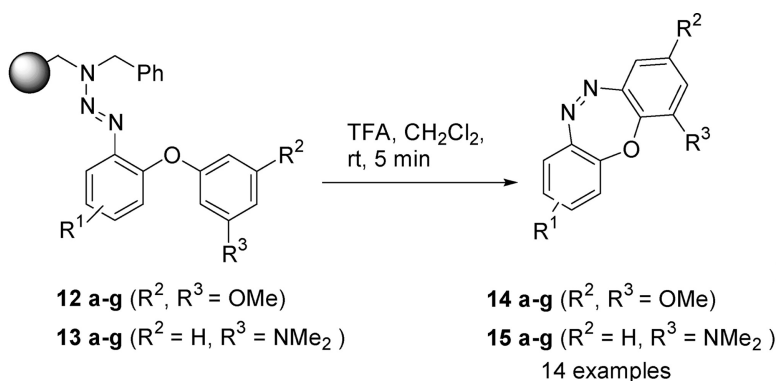
Report

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# Reports

## Syntheses of 5-Oxa-10,11-diazadibenzo[*a,d*]cycloheptenes on Solid Supports

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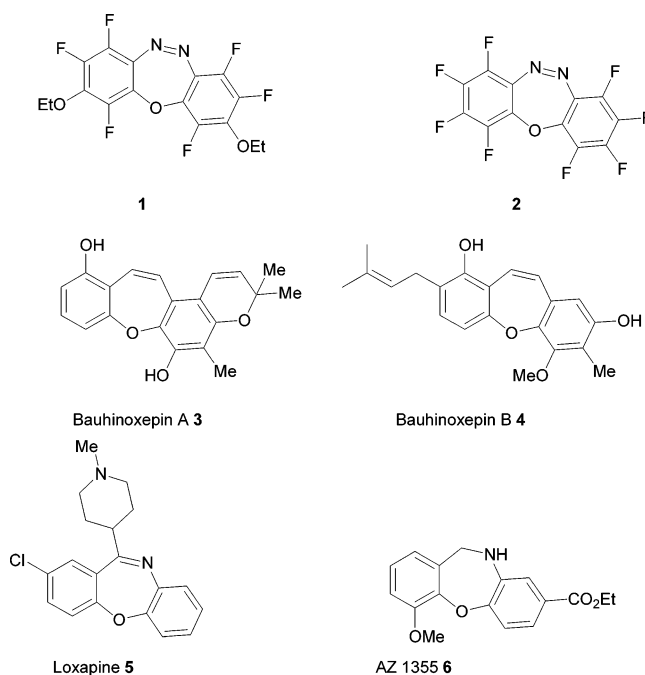
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Benzoannulated nitrogen and oxygen heterocycles are pivotal elements in modern drug discovery programs.<sup>1</sup> Although various structures have been synthesized on solid supports, dibenzoannulated structures, such as 5-oxadibenzocycloheptenes, are not very common. This class of benzoannulated heterocycles is not very often found in natural or synthetic products, with the notable exception of 2-chloro-11-(1-methylpiperidin-4-yl)-dibenzo[*b,f*][1,4]oxazepine (Loxapine) (**5**) and AZ 1355 (**6**). However, they are druglike molecules due to the fact that they mimic related compounds having a similar planar structure. During the search for inhibitors of the 17 $\alpha$ -hydroxylase-C<sub>17,20</sub>-lyase and the testosteron-5 $\alpha$ -reductase, which are target enzymes for the development of drugs used for the treatment of prostate cancer caused by hormones, the two fluorinated heterocycles **1** and **2**, shown in Figure 1, were identified.<sup>2</sup> A few carbon analogues which showed interesting biological activity were found, as well. For example, in the last year, two new antimycobacterial dibenzoxepines **3** and **4** were identified.<sup>3</sup> Bauhinoxepin A (**3**) und B (**4**) were isolated from the roots of *Bauhinia saccocalyx* (Figure 1).

Even today, there are only a few syntheses for 5-oxa-10,11-diazadibenzo[*a,d*]cycloheptenes described.<sup>4–7</sup> In all the systems described up to now, the ether bridge was formed first, then a nitro group was reduced to the free amine and diazotized to the diazonium salt. The closing of the rings yielded very colorful products. In this Report, we present the solid-phase synthesis of various 5-oxa-10,11-diazadibenzo[*a,d*]cycloheptenes.

Recently, we reported the efficient syntheses of diaryl ethers on solid supports using a Ullmann–Nicolaou reaction.<sup>8,9</sup> To devise a two-step synthesis of 5-oxa-10,11-diazadibenzo[*a,d*]cycloheptenes, different anilines **8a–g** were immobilized as triazenes on Merrifield-type polystyrene



**Figure 1.** Biologically active 5-oxa-10,11-diazadibenzo[*a,d*]cycloheptenes and two carbon analogues.

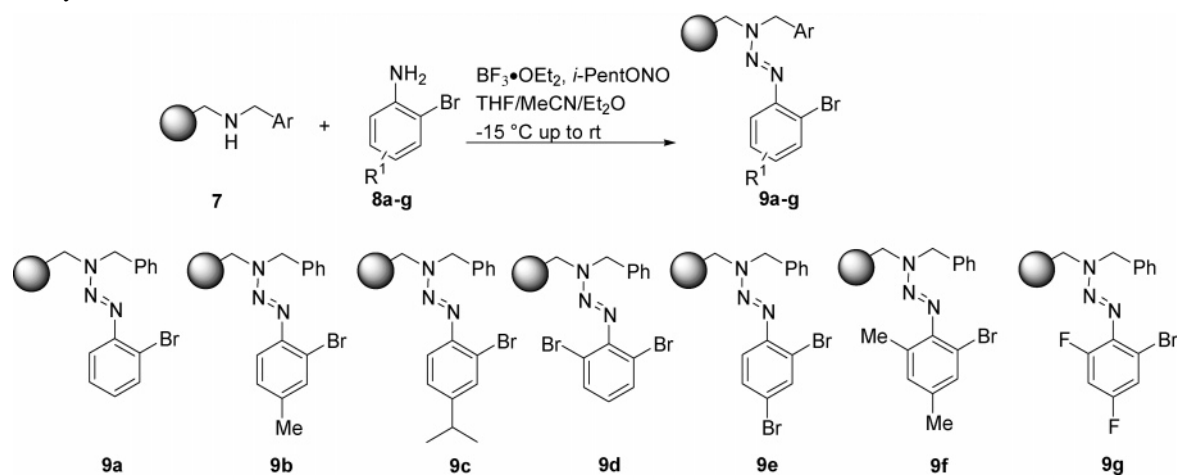
resin. In this way, seven triazene T1 resins, **9a–g**, were prepared (Scheme 1).

The diaryl ether moiety was constructed efficiently by coupling with 3,5-dimethoxyphenol (**10**) and 3-dimethylaminophenol (**11**), respectively, under basic copper conditions (Scheme 2). Optimization of the coupling procedure, which is applicable for various phenols and aryl halides, revealed that 5 equiv of the phenol and 5 equiv of the copper reagents provides full conversion. The excess of reagents, any byproducts derived from premature cleavage from the resin (i.e., anilines), and the remaining copper salts can be removed via an improved washing procedure (see Experimental Section). It should be noted that since this copper-mediated procedure using commercially available reagents is compatible with many functional groups found in complex molecules,<sup>8</sup> tolerates base-sensitive amino acids, and works with electron-rich aryl bromides at temperatures compatible with polystyrene chemistry (below 100 °C), no efforts have been made to use different methods devised in the past years, in particular, using a diminished amount of copper salts.<sup>10</sup> Due to the quite robust nature of the triazene linker, these new methods might work equally well. However, the Ullmann–Nicolaou procedure tolerates halides being in meta or para position of the triazene moiety (e.g., resin **9e**), giving rise to halodiaryl ethers, which can be used for further cross-coupling reactions.<sup>9</sup> Double coupling is possible (resin **9d**).

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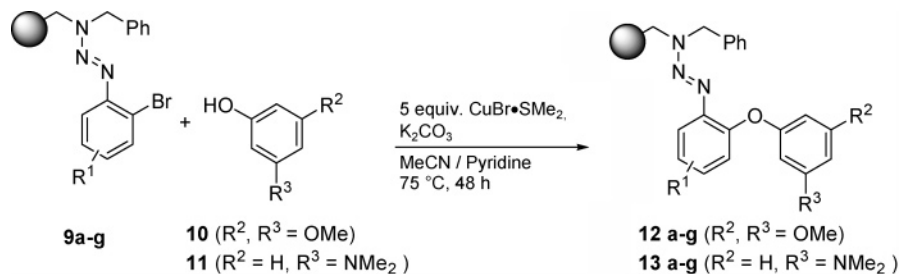
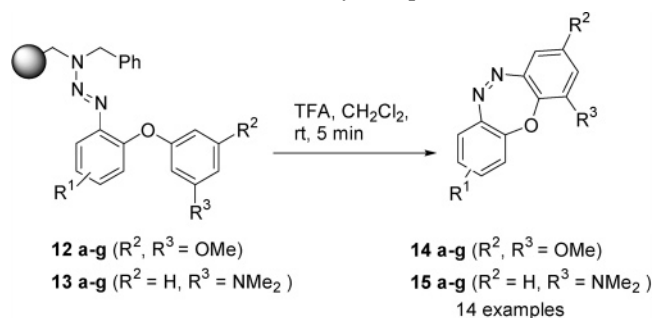
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**Scheme 1.** Syntheses of the Different Triazene T1 Resins**Table 1.** Yielded Heterocycles through Intramolecular Aza Coupling<sup>a</sup>

Entry	Resin	Phenol	Product	Yield (%) <sup>b</sup>	Entry	Resin	Phenol	Product	Yield (%) <sup>b</sup>
1				87	8				80
2				81	9				76
3				92	10				92
4				96	11				85
5				79	12				81
6				47	13				82
7				88	14				87

<sup>a</sup> See Scheme 3. All reactions were performed with 5 equiv of the copper reagent at 75 °C in acetonitrile/pyridine 3/1. The cleavage was performed at room temperature. <sup>b</sup> Isolated yields based on the loading of resins 9a–g.

**Scheme 2.** Nicolaou–Ullmann Reaction on Solid Supports**Scheme 3.** Cyclative Cleavage to Yield the 5-Oxa-10,11-diazadibenzo[*a,d*]cycloheptenes

The cleavage to the heterocycles took place at room temperature in dichloromethane and 5% trifluoroacetic acid. First, the diazonium salt was formed, which attacks the arene system, yielding the heterocycles **14** and **15**. This reaction demonstrated a novel cyclative cleavage reaction. The new heterocycles were intensely colorful, whereas the ones created by the dimethoxy substitution were yellow, and the ones having a dimethylamino substitution were deep red (Scheme 3).<sup>11</sup>

The solvent was removed under reduced pressure, and the crude products were purified by preparative TLC. All products had purities higher than 95% (NMR, GC). The results are summarized in Table 1. In most cases, the corresponding heterocycles were isolated in good global yields. Together with the results of our previously described synthesis of functionalized diaryl ethers,<sup>9</sup> it is apparent that at least two meta alkoxy or one amino functionality must be present in the aryl moiety that is the nucleophile in the intramolecular azo coupling. In the diazonium salt, electron-deficient and -rich arenes are tolerated.

In summary, we have developed a high-yielding solid-phase access to 5-oxa-10,11-diaza-dibenzo[*a,d*]cycloheptenes that is more efficient than the previously used liquid-phase approaches.

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**Supporting Information Available.** Experimental details and spectroscopic and analytical data for all products not described in the text. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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