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New Heterocyclic Precursors for Thermal Generation of Reactive, Electron-Rich 1,2-Diaza-1,3-butadienes

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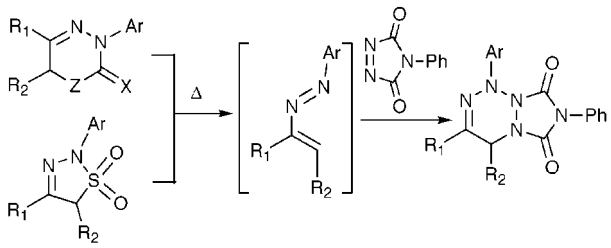
ABSTRACT



The preparation and thermolysis of new stable heterocyclic precursors of 1,2-diaza-1,3-butadienes is described. The resulting reactive diazadienes are trapped in situ with *N*-phenyldiazamaleimide. The effect of precursor structure on the temperature at which the diazadienes are generated is discussed.

The chemistry of 1,2-diaza-1,3-butadienes **1**, or azoalkenes as these substances are also known, has been under active investigation for a number of years.[1] The reactivity of these intermediates, either isolated or generated in situ, has been shown to include the addition of a variety of nucleophiles.[2] Azadienes **1** also undergo ready cycloaddition with a structurally diverse group of electron-rich and electron-deficient olefins, as well as 1,3-dipoles, and afford as products a variety of heterocyclic ring systems.[3]

The usual methods of synthesis of azadienes such as **1** involve either (1) based-induced dehydrohalogenation of α-halohydrazones obtained either by halogenation of hydrazones or conversion of α-halo carbonyl derivatives to the hydrazones[4] or (2) oxidation of hydrazones with various oxidizing agents such as I_2 or HgO.[5] While conjugated, electron-deficient examples of **1** (R_1 = EWG or Ar or R_2 = alkyl, Ar, or EWG) have been prepared (often in low yield and purity), those cases bearing as R_2 small alkyl or electron donor groups tend to undergo ready dimerization unless intercepted by an appropriate coreactant (Figure 1).[6] Thus, the aforementioned synthetic methods become problematic in these latter cases, since the azadienes must often be generated in the presence of nucleophilic bases or solvents. Byproducts from their generation can be difficult to remove which can compromise subsequent transformations.

In connection with our interest in developing environmentally benign methods for preparation of heterocyclic

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(2) (a) Arcadi, A.; Attanasi, O. A.; De Crescentini, L.; Rossi, E.; Serra-Zanetti, F. *Synthesis* **1996**, 533−6. (b) Arcadi, A.; Attanasi, O. A.; Liao, Z.; Serra-Zanetti, F. *Synthesis* **1994**, 605−8. (c) Schantl, J. G.; Karpellus, P.; Prean, M. *Tetrahedron* **1982**, *38*, 2643−52.

(3) (a) Gilchrist, T. L.; Sanchez Romero, O. A.; Wasson, R. C. *J. Chem. Soc., Perkin Trans. 1* **1989**, 353−9. (b) Sommer, S. *Angew. Chem.* **1979**, *91*, 756−7. (c) Sommer, S. *Chem. Lett.* **1977**, 583−6. (d) Zelenin, K. N.; Nikitin, V. A.; Anodina, N. M. *Khim. Geterotsikl. Soedin.* **1973**, 124−8.

(4) (a) Gilchrist, T. L.; Sanchez Romero, O. A.; Wasson, R. C. *J. Chem. Soc., Perkin Trans. 1* **1989**, 353−9. (b) Attanasi, O. A.; Grossi, M.; Mei, A.; Serra-Zanetti, F. *Org. Prep. Proced. Int.* **1988**, *20*, 408−14. (c) Attanasi, O.; Filippone, P.; Mei, A.; Serra-Zanetti, F. *J. Heterocycl. Chem.* **1985**, *22*, 1341−3.

(5) (a) Schantl, J. *Tetrahedron Lett.* **1971**, 153−6. (b) Schantl, J. *Monatsh. Chem.* **1972**, *103*, 1705−17. (c) Schantl, J. *Monatsh. Chem.* **1972**, *103*, 1718−29.

(6) (a) Schantl, J. *Monatsh. Chem.* **1974**, *105*, 220−8. (b) Schantl, J. *Monatsh. Chem.* **1974**, *105*, 314−21. (c) Schantl, J. *Monatsh. Chem.* **1974**, *105*, 322−6.

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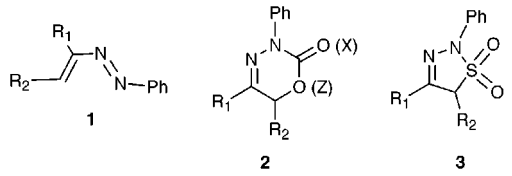


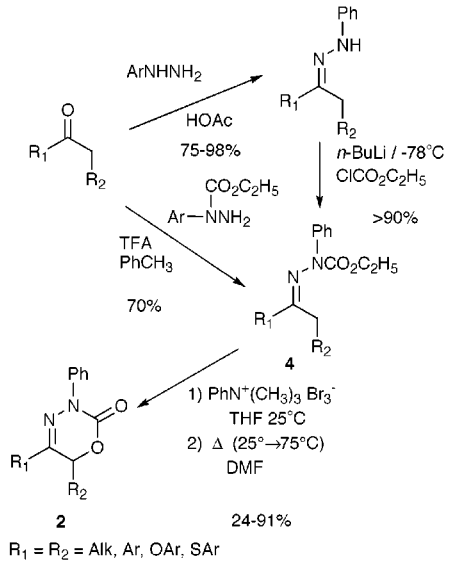
Figure 1.

systems using transition metal catalysis, we sought to develop general methods for generation of the required azadienes **1** under controlled conditions in the absence of nucleophiles and other undesirable byproducts.

We identified two general classes of precursors exemplified by the 3,6-dihydro-1-oxa-3,4-diazin-2-ones **2** and 2,5-dihydro-1,2,3-thiadiazole-1,1-dioxides **3** (Figure 1), which upon thermal extrusion of CO_2 and SO_2, respectively, should afford the reactive azadienes **1** suitable for further transformations. Examination of the literature revealed that few examples of either class **2** or **3** had been reported.[7,8] No thermal chemistry had been reported for either, although related derivatives of **2** lacking substitution at position 3 were reported to undergo thermal decomposition via tautomerization to 5,6-dihydro-1-oxa-3,4-diazin-2-ones and loss of both N_2 and CO_2, affording olefins.[7]

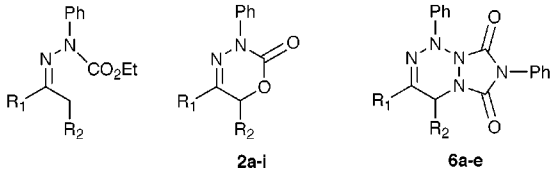
We have developed two general routes to the oxadiazinones **2** via the *N*-carbethoxyhydrazones **4** as shown in Scheme 1. Acylhydrazones **4**, prepared by either of the

Scheme 1



indicated routes from known hydazine derivatives,[9] were brominated with phenyltrimethylammonium perbromide (PTAB), and the resulting sensitive bromo hydrazones underwent ring closure with expulsion of EtBr spontaneously or upon mild heating in DMF. Several examples prepared in this manner are depicted in Table 1.

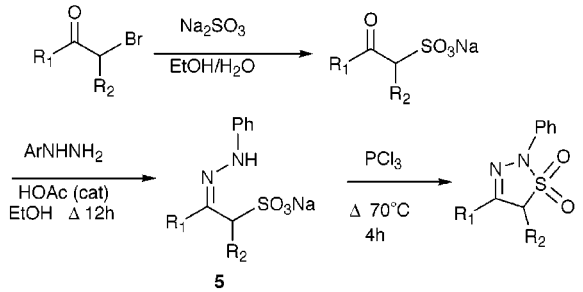
Table 1. Oxadiazinones **2** and Diels–Alder Adducts **6**



substrate	yield (%) **2a–i**	*T* (°C)	yield (%) **6a–e**
$R_1 = R_2 =$ Ph	72	140	84
$R_1 =$ Ph	45	110	98
$R_2 =$ OPh			
$R_1 =$ Ph	54	110	95
$R_2 =$ OTol*o*			
$R_1 =$ Ph	81	140	99
$R_2 =$ OTol*p*			
$R_1 =$ Ph	82		
$R_2 =$ OPhCl*o*			
$R_1 =$ Ph	86	162	79
$R_2 =$ OPhNO2*o*			
$R_1 =$ Ph	60		
$R_2 =$ SPh			
$R_1 =$ tBu	90		
$R_2 = CH_3$			
$R_1 = CH_3$	24		
$R_2 =$ Ph			

With respect to the thiadiazole dioxides **3**, we employed the method of Mazak, involving PCl_3-induced ring closure of hydrazones of β-ketosulfonic acid salts **5**, as shown in Scheme 2.[8] The precursor salts are readily available from

Scheme 2



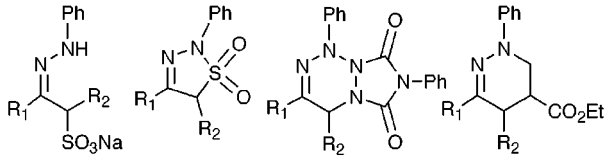
α-bromo ketones via treatment with Na_2SO_3. Several examples prepared in this manner are depicted in Table 2.

(7) Rosenblum, M. Nayak, V.; Das Gupta, S. K.; Longrow, A. *J. Am. Chem. Soc.* **1963**, *85*, 3874–78.

(8) (a) Mazak, P.; Suszko, J. *Rocz. Chem.* **1929**, *9*, 431–33. (b) Mazak, P.; Suszko, J. *Bull. Intern. Acad. Pol.* **1929A**, 131–142. (c) Terent'ev, A. P.; Preobrazhenskaya, M. N. *Zh. Obshch. Khim.* **1956**, *26*, 3468–3475.

(9) (a) El-Haddad, M. R.; Ferwanah, A. E.-R. S.; Awadallah, A. M. *J. Prakt. Chem./Chem.- Ztg.* **1998**, *340*, 623–626. (b) Busch, M.; Limpach, O. *Chem. Ber.* **1911**, *44*, 1573–1583.

Table 2. 1,1-Dioxides **3** and Diels−Alder Adducts **6**



3a-e **6a-c**

substrate	yield (%) **3a−e**	yield (%) **6a−c**	yield (%)
$R_1 = CH_3$ $R_2 = H$	60	74	34
$R_1 = Ph$ $R_2 = H$	78	92	59
$R_1 = Ph$ $R_2 = Ph$	80	85	
$R_1 = PhCl$*p* $R_2 = H$	70		
$R_1 = Ph$ $R_2 = OPh$	20		

With routes to substrate classes **2** and **3** in hand, we examined their thermal chemistry. On the basis of EI mass spectroscopy of a number of derivatives of **2** and **3**, all of which exhibited abundant fragment ions (often the base peak) corresponding to loss of CO_2 or SO_2 respectively, we believed that generation of derivatives of **1** would prove facile. Since the classes of azadienes **1** of major interest to us were expected to be too unstable for isolation, we decided to assess the efficiency of generation of the azadienes **1** by effecting thermolysis in the presence of suitable dienophiles as has been commonly employed in previous studies.[10]

When oxadiazinone **2** ($R_1 = R_2 = Ph$) is heated in the presence of *N*-phenylmaleimide (5 equiv) at 140 °C in xylene followed by chromatographic purification, the Diels−Alder adduct **6** ($R_1 = R_2 = Ph$) was obtained in 84% yield (Scheme 3).

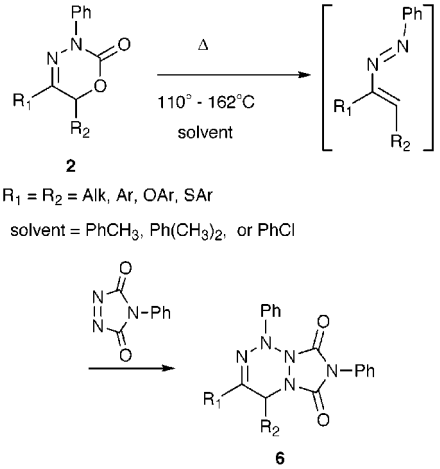
Likewise, the other examples listed in Table 1 afforded the expected adducts in 79−99% yield. The onset of decomposition of derivatives of **2** appeared somewhat sensitive to the structure of R_2. The more conjugating and/or electron-deficient R_2, the slower the loss of CO_2, necessitating use of higher temperatures, as would be expected for such electronically stabilizing substituents.

The dioxides **3** underwent extrusion of SO_2 somewhat more readily than the oxadiazenes **2**. As shown in Table 2, heating the dioxides **3** in toluene readily generated the intermediate azadienes **1** which were trapped in excellent yields (74−92%) with *N*-phenylmaleiimide, as well as with ethyl acrylate (34−59% unoptimized).

However, our principal goal in undertaking the chemistry was to identify methods of generation of **1** compatible with transition metal catalysts (e.g., Pd(0)). Thus, we attempted to lower further the temperature at which the generation of the azadienes **1** would take place, since high temperatures

(10) Allcock, S. J.; Gilchrist, T. L.; King, F. D. *Tetrahedron Lett.* **1991**, *32*, 125−8.

Scheme 3



2

$R_1 = R_2 =$ Alk, Ar, OAr, SAr

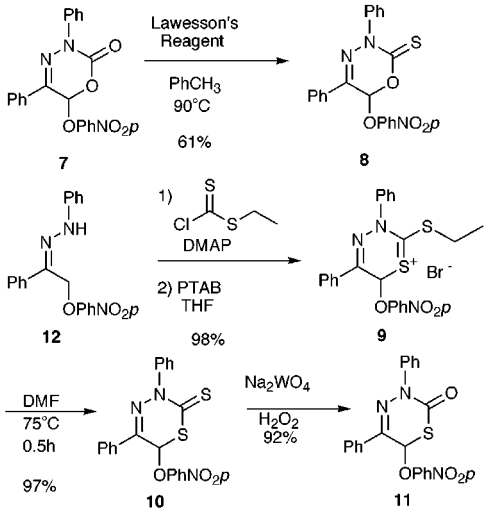
solvent = $PhCH_3$, $Ph(CH_3)_2$, or PhCl

6

can result in catalyst decomposition. Since it was apparent that the synthetic route to the oxadiazinones was more general and robust, we chose to prepare the dithio and mixed oxygen and sulfur analogues (**2**, X = S or O and Z = O or S). We hypothesized that the weaker C−S bonds might reduce the temperature required for onset of the extrusion reaction.

The thio analogues were prepared on the basis of the least reactive derivative of **2** (R_2 = $OPhNO_2$*p*) as shown in Scheme 4.

Scheme 4



7 **8** **12** **9** **10** **11**

Treatment of **7** with Lawesson's reagent afforded thione **8** in 61% yield (unoptimized).[11] Dithio derivative **10** and thiolactam **11** were obtained from hydrazone **12** by analogy to **2**. Acylation of **12** with ethyl chlorodithioformate followed

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by bromination with PTAB afforded the isolable salt **9** in 98% overall yield. Mild heating of **9** in DMF expelled EtBr, providing **10** in 97% yield. Tungsten-catalyzed hydrogen peroxide oxidation of **10** then afforded **11** (92%).[12]

Our expectations regarding the ease of thermolysis of **8** and **10**−**11** were realized. Heating **8**, **10**, and **11** in toluene (110 °C) in the presence of 5 equiv of *N*-phenylmaleimide, as described above, afforded the expected adduct **6** (R_1 = Ph, R_2 = $OPhNO_2$) in 80−85% yield. Qualitatively, thione **8** appeared the fastest although, in each case, extrusion took place approximately 50 °C lower than the oxygen analogues **2**, corresponding to an estimated 30-fold increase in rate.

In the accompanying Letter,[13] we detail our efforts to employ the azadienes generated by our new methods as intermediates in a new Pd(0)-catalyzed synthesis of pyrazolones.

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Supporting Information Available: General experimental procedures and characterization data for **2a**, **2f**, **3k**, **4a**, **4f**, **6a**, **6c**, **6f**, **6k**, **7, 9**, and **10**. This information is available free of charge via the Internet at http://pubs.acs.org.

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(12) Hanefeld, W.; Schlitzer, M. *Arch. Pharm. (Weinheim, Ger.)* **1994**, *327*, 413−15.

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