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# Synthesis, Characterization, and Rapid Cycloadditions of 5-Nitro-1,2,3-triazine

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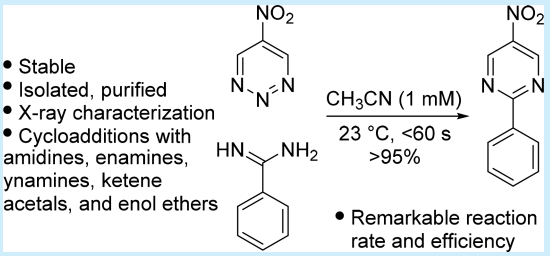
Supporting Information

**ABSTRACT:** The synthesis, characterization, and a study of the cycloaddition reactions of 5-nitro-1,2,3-triazine (**3**) are reported. The electron-deficient nature of **3** permits rapid cycloaddition with a variety of electron-rich dienophiles, including amidines, enamines, enol ethers, ynamines, and ketene acetals in high to moderate yields. $^1$H NMR studies of a representative cycloaddition reaction between **3** and an amidine revealed a remarkable reaction rate and efficiency (1 mM, <60 s, $CD_3CN$, 23 °C, >95%).




The inverse electron demand Diels−Alder reaction of heterocyclic azadienes often provides an effective strategy for the preparation of highly substituted heterocyclic scaffolds of synthetic and medicinal chemistry interest.[1] Over the course of the years, we have systematically explored the cycloaddition reactions of 1,2,4,5-tetrazines,[2] 1,2,4-triazines,[3] 1,3,5-triazines,[4] 1,3,4-oxadiazoles,[5] and 1,2-diazines,[6] resulting in the development of cycloaddition methodology that is now widely employed.[7−9] The facility of these cycloadditions, coupled with the prevalence of heterocyclic motifs in important natural products, led to our use of the reactions as the key steps in a series of natural product total syntheses, including the antitumor antibiotics streptonigrin[10] and lavendamycin,[11] prodigiosin,[12] isochrysohermidin,[13] ningalin A,[14] CC-1065,[15] bleomycin A2,[16] and vinblastine.[17] More recently, the inverse electron demand Diels−Alder reactions of such heterocyclic azadienes have become a cornerstone of modern bioorthogonal bioconjugation techniques, along with click chemistry.[18]

Recently, our efforts have begun to define the previously unexplored rich cycloaddition chemistry available to 1,2,3-triazines (Figure 1).[19] These studies have included an examination of the synthesis and reaction scope of 1,2,3-triazines bearing electron-rich and electron-deficient substituents with electronically consonant and dissonant positioning, in addition to that of the parent 1,2,3-triazine.[19a−d] Their use as key steps in the total syntheses of P-3A,[16] (−)-pyrimidoblamic acid,[16] dihydrolysergic acid,[19e] dihydrolysergol,[19e] methoxatin,[19f] and their heterocyclic analogues have been reported. During the course of these studies, the first general method for catalysis of the inverse electron demand Diels−Alder reaction of heterocyclic azadienes by solvent hydrogen bonding was disclosed.[19f]

A growing, although still limited, number of electron-deficient 1,2,3-triazines have now been synthesized and examined, although 5-nitro-1,2,3-triazine (**3**) has yet to be prepared. Only one reference to nitrated 1,2,3-triazines was found, in which the as-yet theoretical compounds were computationally examined.[20] Our own simple semiempirical computational studies (AM1, MNDO) of 5-nitro-1,2,3-triazine (**3**) revealed its extraordinarily low lowest unoccupied molecular orbital (LUMO) energy (−1.70 eV to −1.59 eV), compared to those of both the parent 1,2,3-triazine **1** and **2**, which is the most reactive 1,2,3-triazine disclosed to date.[19] This suggested that **3**, if capable of being prepared, would be highly reactive in inverse electron demand Diels−Alder reactions (Figure 2). In addition, Mulliken population analysis

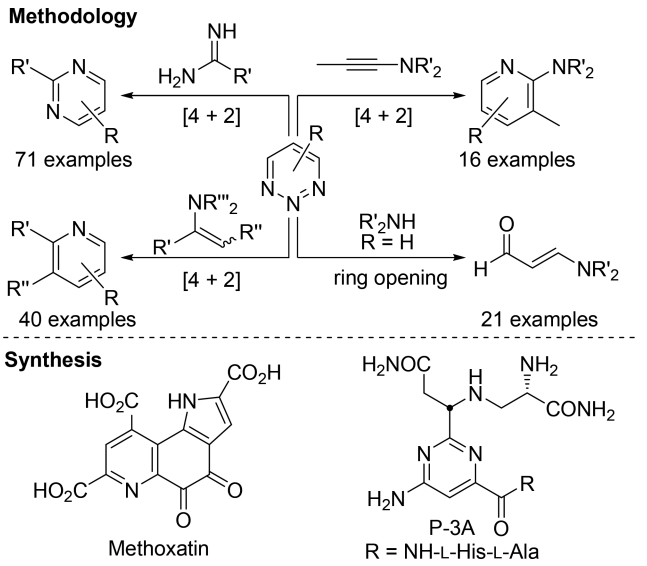



**Figure 1.** Selected previous studies of 1,2,3-triazines.

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also revealed a high degree of polarization, predicting a susceptibility to C4 nucleophilic attack.

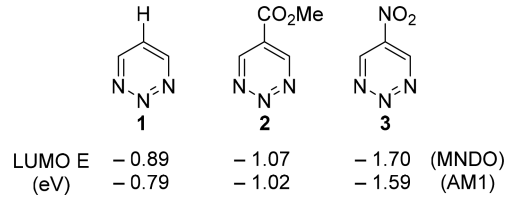
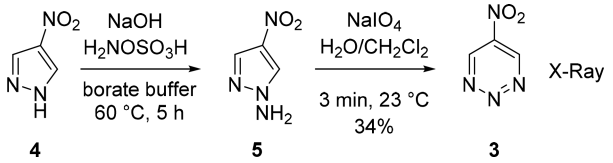



**Figure 2.** Computational studies.

As part of an effort to expand the number of accessible monocyclic 1,2,3-triazines, and to more clearly define their stability characteristics, herein we disclose the successful synthesis of 5-nitro-1,2,3-triazine (**3**), its spectroscopic and X-ray characterization, and an initial survey of its cycloaddition reaction scope and rapid cycloaddition reaction rate.

Multigram scale *N*-amination of 4-nitropyrazole (**4**) was accomplished according to the procedure of Vinogradov and co-workers,[21] which takes advantage of a borate buffer system to ensure the deprotonation of starting material in the presence of the acidic aminating reagent (Scheme 1). Recrystallization of

**Scheme 1. Synthesis of 5-Nitro-1,2,3-triazine (3)**




the crude residue from water afforded the *N*-aminopyrazole **5**, which could be stored indefinitely at −30 °C without incident. Upon submission of **5** to Igeta's biphasic oxidative ring expansion conditions,[22] only trace quantities of 5-nitro-1,2,3-triazine (**3**) could be observed by $^1$H NMR. Although **3** was rapidly formed under the reaction conditions, its extended exposure to the reaction aqueous phase appeared to result in its consumption. After significant optimization efforts, a modified oxidative ring expansion protocol was developed, which minimized the exposure of **3** to water. This protocol, which involves shaking the biphasic reaction mixture in a separatory funnel for 3 min, followed by rapid phase separation and drying of the organic layer, was successful in providing crude residues consisting largely of the desired 1,2,3-triazine **3**. Elution of the crude material through a short plug of $SiO_2$ afforded an acceptable yield of pure 5-nitro-1,2,3-triazine (**3**), provided that the exposure of **3** to $SiO_2$ was minimized (<5 min). 5-Nitro-1,2,3-triazine (**3**), whose structure was characterized spectroscopically as well as in a single crystal X-ray structure determination, exists as a moisture-sensitive yellow crystalline solid that can be stored under $N_2$ or Ar at 4 °C for up to 100 days without observable decomposition ($^1$H NMR).[23]

It was anticipated that **3** would react with free-based amidines with C4/N1 regioselectivity to afford the corresponding pyrimidines in high yields.[19] Indeed, reaction of **3** with amidine **6f** under typical conditions (1.5 equiv **3**, $CH_3CN$ (0.15 M), 23 °C, 5 min, 50%) afforded the corresponding pyrimidine product **7f**, albeit in moderate yield with immediate evolution of $N_2$ and obvious nonproductive consumption of **3**. Exploration of reaction conditions designed to exert more control over the vigorous reaction revealed that either low-temperature or more-dilute reaction conditions improved the conversions, with dilute conditions providing superior, near-quantitative yields of the product pyrimidine in mere seconds.

With effective conditions for the cycloaddition of **3** and amidines defined, an examination of the reaction scope was conducted (Figure 3). The cycloadditions proceeded rapidly

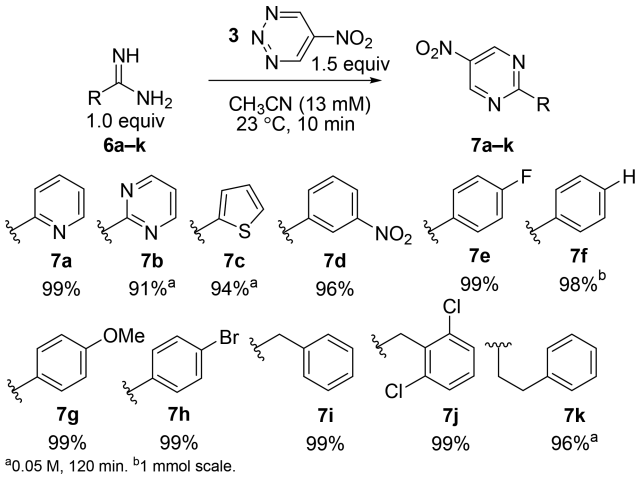



**Figure 3.** Reaction of **3** with amidines.

and afforded the product pyrimidines **7a**−**7k** in excellent yields under extraordinarily mild reaction conditions ($CH_3CN$, 13 mM, 23 °C, <10 min).[24] While the remarkable reaction rates make even relative rate comparisons challenging, there does appear to be at least a qualitative relationship where electron-rich amidines (e.g., **6g**) react most rapidly.

The remarkably rapid rate of cycloaddition between 5-nitro-1,2,3-triazine (**3**) and amidines was examined in greater detail with **6f**. As shown in Figure 4, the cycloaddition reaction proceeded in near-quantitative yield at concentrations as low as 100 $\mu$M, with a 10 $\mu$M reaction still capable of providing detectable amounts of pyrimidine product. Further qualitative study of the reaction conducted at 1 mM ($CD_3CN$) by $^1$H NMR revealed that the reaction is almost complete within 10 s and fully complete in ca. 60 s, which is a rate well beyond the acceptable range for even bioorthogonal bioconjugation reactions.[18] Although it is not clear whether the reactions represent direct [4 + 2] cycloadditions or stepwise addition-cyclization reactions, the rates, and especially the efficiencies, of the reactions are extraordinary.

Enamines represent a second useful class of electron-rich dienophiles capable of reaction with 1,2,3-triazines to afford substituted pyridine products derived from regioselective cycloaddition across C4/N1.[19] Exploration of the reaction of 5-nitro-1,2,3-triazine (**3**) with enamine **8** established the optimized reaction conditions, which were applied to a suite of representative enamine cycloadditions (Figure 5). The reactions proceed smoothly to afford the corresponding pyridines (**13**−**15**, **19**−**21**, **23**) in good to moderate yields.[25] It is important to note that the elevated reaction temperature and extended reaction times are unnecessary to observe the initial cycloaddition of **3** with enamines, but rather are required to promote the elimination of pyrrolidine or morpholine to afford the product pyridines. Efforts to improve the cycloaddition yields through solvent hydrogen bond catalysis[19f] were



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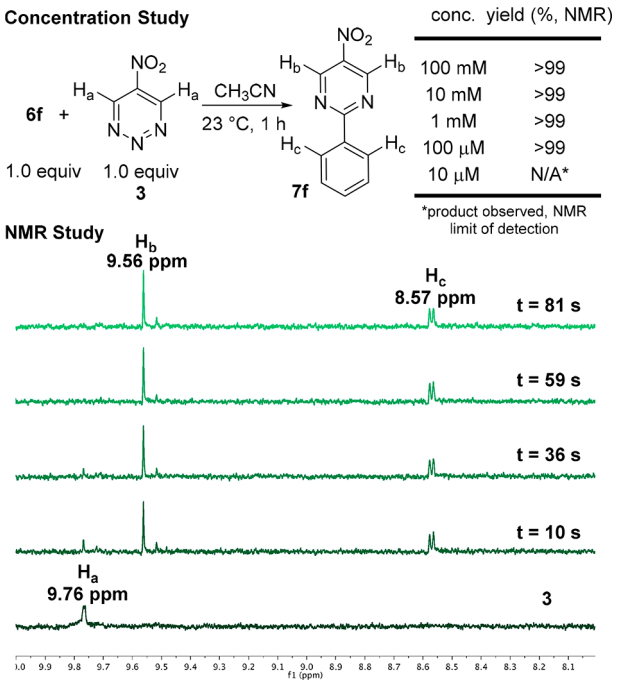
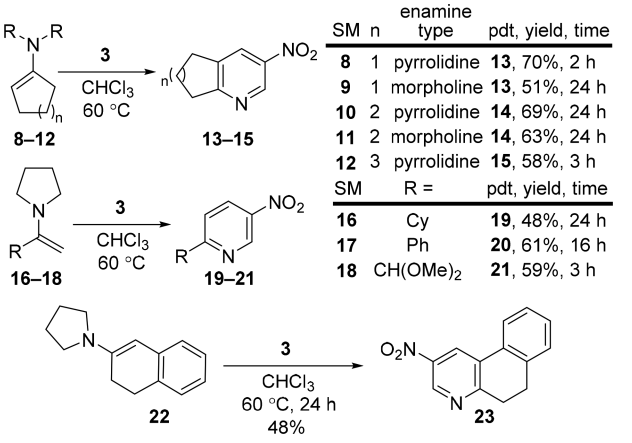



**Figure 4.** Concentration (top) and $^1$H NMR studies at 1 mM and 23 °C (bottom) of the reaction of **6f** (1 equiv) and **3** (1 equiv) in $CD_3CN$.




| SM | n | enamine type | pdt, yield, time |
|---|---|---|---|
| 8 | 1 | pyrrolidine | **13**, 70%, 2 h |
| 9 | 1 | morpholine | **13**, 51%, 24 h |
| 10 | 2 | pyrrolidine | **14**, 69%, 24 h |
| 11 | 2 | morpholine | **14**, 63%, 24 h |
| 12 | 3 | pyrrolidine | **15**, 58%, 3 h |
| SM | | R = | pdt, yield, time |
| 16 | | Cy | **19**, 48%, 24 h |
| 17 | | Ph | **20**, 61%, 16 h |
| 18 | | $CH(OMe)_2$ | **21**, 59%, 3 h |

**Figure 5.** Reaction of **3** with enamines.

not successful, as **3** rapidly and nonproductively reacts with protic solvents.

Additional dienophiles known to react with 1,2,3-triazines were also examined (Figure 6).[19] Ketene acetals and ynamines

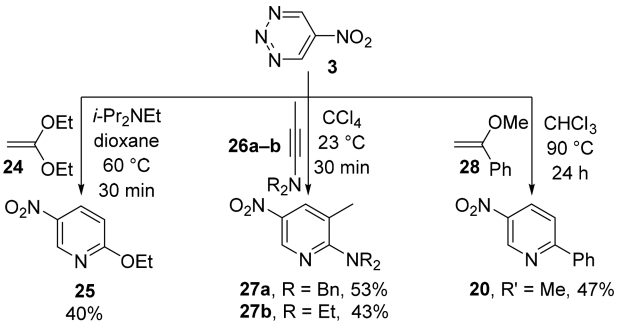



**Figure 6.** Reaction of **3** with other dienophiles.

undergo rapid reaction with **3** to afford the product pyridines derived from regioselective cycloaddition across C4/N1.[26] *O*-Methyl enol ethers also undergo reaction with **3**, but only under more forcing thermal conditions.[25]

Herein, the synthesis, characterization, and survey of the cycloaddition reactions of 5-nitro-1,2,3-triazine (**3**) are disclosed. Despite its anticipated reactivity, **3** could be prepared, purified by chromatography, fully characterized, and stored at 4 °C for several months. 1,2,3-Triazine **3** was found to participate in cycloaddition reactions with amidines, enamines, enol ethers, ynamines, and ketene acetals in high to moderate yields. The qualitative rate of the amidine cycloaddition reaction with **3** was examined and found to be extraordinarily fast and efficient, being competitive with even the tetrazine reactions used in bioorthogonal ligation reactions.[18]

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b00825.

Full experimental details and $^1$H NMR spectra (PDF)

### Accession Codes

CCDC 1818968 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.; fax: +44 1223 336033.

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### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

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## ■ REFERENCES

(1) (a) Boger, D. L. *Tetrahedron* **1983**, *39*, 2869. (b) Boger, D. L. *Chem. Rev.* **1986**, *86*, 781.

(2) (a) Carboni, R. A.; Lindsey, R. V. *J. Am. Chem. Soc.* **1959**, *81*, 4342. (b) Sauer, J.; Wiest, H. *Angew. Chem., Int. Ed. Engl.* **1962**, *1*, 269. (c) Boger, D. L.; Coleman, R. S.; Panek, J. S.; Yohannes, D. *J. Org. Chem.* **1984**, *49*, 4405. (d) Boger, D. L.; Panek, J. S.; Coleman, R. S.; Sauer, J.; Huber, F. X. *J. Org. Chem.* **1985**, *50*, 5377. (e) Boger, D. L.; Sakya, S. M. *J. Org. Chem.* **1988**, *53*, 1415. (f) Boger, D. L.; Schaum, R. P.; Garbaccio, R. M. *J. Org. Chem.* **1998**, *63*, 6329. (g) Soenen, D. R.; Zimpleman, J. M.; Boger, D. L. *J. Org. Chem.* **2003**, *68*, 3593.



DOI: 10.1021/acs.orglett.8b00825
*Org. Lett.* XXXX, XXX, XXX−XXX

(3) (a) Steigel, A.; Sauer, J. *Tetrahedron Lett.* **1970**, *11*, 3357. (b) Neunhoeffer, H.; Fruhauf, H.−W. *Leibigs Ann. Chem.* **1972**, *758*, 120. (c) Boger, D. L.; Panek, J. S. *J. Org. Chem.* **1981**, *46*, 2179. (d) Boger, D. L.; Panek, J. S.; Meier, M. M. *J. Org. Chem.* **1982**, *47*, 895.
(4) (a) Neunhoeffer, H.; Bachmann, M. *Chem. Ber.* **1975**, *108*, 3877. (b) Boger, D. L.; Schumacher, J.; Panek, J. S.; Mullican, M. D.; Patel, M. *J. Org. Chem.* **1982**, *47*, 2673.
(5) (a) Wilkie, G. D.; Elliott, G. I.; Blagg, B. S. J.; Wolkenberg, S. E.; Soenen, D. R.; Miller, M. M.; Pollack, S.; Boger, D. L. *J. Am. Chem. Soc.* **2002**, *124*, 11292. (b) Elliott, G. I.; Fuchs, J. R.; Blagg, B. S. J.; Ishikawa, H.; Tao, H.; Yuan, Z.-Q.; Boger, D. L. *J. Am. Chem. Soc.* **2006**, *128*, 10589.
(6) (a) Neunhoeffer, H.; Werner, G. *Liebigs Ann. Chem.* **1973**, *1973*, 437. (b) Boger, D. L.; Coleman, R. S. *J. Org. Chem.* **1984**, *49*, 2240. (c) Boger, D. L.; Coleman, R. S. *J. Am. Chem. Soc.* **1987**, *109*, 2717. (d) Kessler, S. N.; Wegner, H. A. *Org. Lett.* **2010**, *12*, 4062. (e) Sumaria, C. S.; Tuerkmen, Y. E.; Rawal, V. H. *Org. Lett.* **2014**, *16*, 3236.
(7) (a) Boger, D. L.; Zhang, M. *J. Am. Chem. Soc.* **1991**, *113*, 4230. (b) Boger, D. L.; Hong, J.; Hikota, M.; Ishida, M. *J. Am. Chem. Soc.* **1999**, *121*, 2471. (c) Boger, D. L.; Wolkenberg, S. E. *J. Org. Chem.* **2000**, *65*, 9120.
(8) (a) Boger, D. L.; Hong, J. *J. Am. Chem. Soc.* **2001**, *123*, 8515. (b) Oakdale, J. S.; Boger, D. L. *Org. Lett.* **2010**, *12*, 1132.
(9) Sears, J. E.; Boger, D. L. *Acc. Chem. Res.* **2016**, *49*, 241.
(10) Boger, D. L.; Panek, J. S. *J. Am. Chem. Soc.* **1985**, *107*, 5745.
(11) Boger, D. L.; Panek, J. S.; Duff, S. R.; Yasuda, M. *J. Org. Chem.* **1985**, *50*, 5790.
(12) Boger, D. L.; Patel, M. *J. Org. Chem.* **1988**, *53*, 1405.
(13) Boger, D. L.; Baldino, C. M. *J. Am. Chem. Soc.* **1993**, *115*, 11418.
(14) Boger, D. L.; Boyce, C. W.; Labroli, M. A.; Sehon, C. A.; Jin, Q. *J. Am. Chem. Soc.* **1999**, *121*, 54.
(15) (a) Boger, D. L.; Coleman, R. S. *J. Am. Chem. Soc.* **1988**, *110*, 1321. (b) Boger, D. L.; Boyce, C. W.; Garbaccio, R. M.; Goldberg, J. A. *Chem. Rev.* **1997**, *97*, 787.
(16) (a) Boger, D. L.; Cai, H. *Angew. Chem., Int. Ed.* **1999**, *38*, 448. (b) Duerfeldt, A. S.; Boger, D. L. *J. Am. Chem. Soc.* **2014**, *136*, 2119.
(17) Sears, J. E.; Boger, D. L. *Acc. Chem. Res.* **2015**, *48*, 653.
(18) (a) Blackman, M. L.; Royzen, M.; Fox, J. M. *J. Am. Chem. Soc.* **2008**, *130*, 13518. (b) Devaraj, N. K.; Weissleder, R.; Hilderbrand, S. A. *Bioconjugate Chem.* **2008**, *19*, 2297. (c) McKay, C. S.; Finn, M. G. *Chem. Biol.* **2014**, *21*, 1075.
(19) (a) Anderson, E. D.; Boger, D. L. *Org. Lett.* **2011**, *13*, 2492. (b) Anderson, E. D.; Boger, D. L. *J. Am. Chem. Soc.* **2011**, *133*, 12285. (c) Anderson, E. D.; Duerfeldt, A. S.; Zhu, K.; Glinkerman, C. M.; Boger, D. L. *Org. Lett.* **2014**, *16*, 5084. (d) Glinkerman, C. M.; Boger, D. L. *Org. Lett.* **2015**, *17*, 4002. (e) Lee, K.; Poudel, Y.; Glinkerman, C. M.; Boger, D. L. *Tetrahedron* **2015**, *71*, 5897. (f) Glinkerman, C. M.; Boger, D. L. *J. Am. Chem. Soc.* **2016**, *138*, 12408. (g) Quiñones, R. E.; Glinkerman, C. M.; Zhu, K.; Boger, D. L. *Org. Lett.* **2017**, *19*, 3568.
(20) Türker, L.; Atalar, T.; Gümüş, S.; Çamur, Y. *J. Hazard. Mater.* **2009**, *167*, 440.
(21) Vinogradov, V. M.; Dalinger, I. L.; Shevelev, S. A. *Mendeleev Commun.* **1993**, *3*, 111.
(22) Itoh, T.; Ohsawa, A.; Okada, M.; Kaihoh, T.; Igeta, H. *Chem. Pharm. Bull.* **1985**, *33*, 3050.
(23) Differential scanning calorimetric measurement (Supporting Information page S61) at 5 °C $min^{-1}$ indicates that **3** does not melt prior to decomposition and has an onset decomposition temperature of 66 °C. From 66 °C to 90 °C, only a small fraction of the compound's total energy is released. Peak heat flow occurs at 113 °C. Overall, **3** releases 4342 J/g of energy over the full temperature range of decomposition (66−272 °C).
(24) (a) Caton, M. P. L.; Hurst, D. T.; McOmie, J. F. W.; Hunt, R. R. *J. Chem. Soc. C* **1967**, 1204. (b) Fanta, P. E.; Hedman, E. A. *J. Am. Chem. Soc.* **1956**, *78*, 1434. (c) Hale, W. J.; Brill, H. C. *J. Am. Chem. Soc.* **1912**, *34*, 82.
(25) (a) Charushin, V. N.; van der Plas, H. C. *Tetrahedron Lett.* **1982**, *23*, 3965. (b) Marcelis, A. T. M.; van der Plas, H. C. *Tetrahedron* **1989**, *45*, 2693. (c) Tohda, T.; Eiraku, E.; Nakagawa, T.; Usami, Y.; Ariga, M.; Kawashima, T.; Tani, K.; Watanabe, H.; Mori, Y. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 2820.
(26) Räth, C. *Justus Liebigs Ann. Chem.* **1930**, *484*, 52.



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