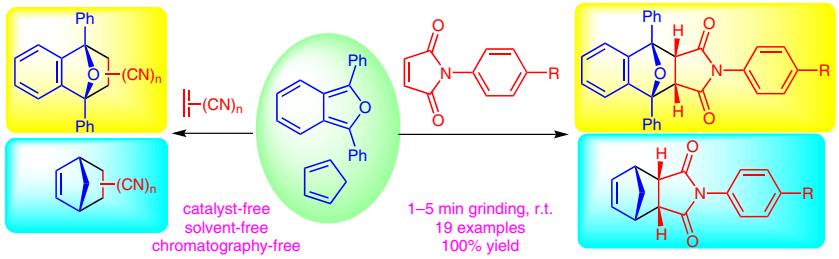
Synlett J. Agarwal et al. Letter

# Mechanochemical Grinding Diels–Alder Reaction: Highly Efficient and Rapid Access to Bi-, Tri-, and Tetracyclic Systems

**Jyoti Agarwal**
**Rashmi Rani**
**Rama Krishna Peddinti***

Department of Chemistry, Indian Institute of Technology Roorkee, Roorkee-247667, Uttarakhand, India
rkpedfcy@iitr.ac.in
ramakpeddinti@gmail.com




Received: 07.01.2017
Accepted after revision: 22.02.2017
Published online: 15.03.2017
DOI: 10.1055/s-0036-1558970; Art ID: st-2017-d0017-l

**Abstract** Grinding of various electron-deficient dienophiles with diverse dienes in a pestle and mortar for 1–15 minutes afforded the corresponding Diels–Alder adducts in quantitative yields under catalyst-free and solvent-free conditions, without the necessity for any purification steps.

**Key words** solvent-free reaction, Diels–Alder reaction, cycloaddition, polycyclic compounds, green chemistry

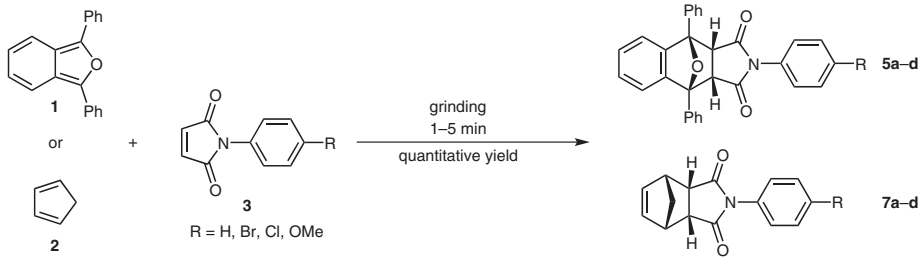
Mechanochemical grinding reactions have drawn attention from scientists in the areas of organic chemistry, supramolecular chemistry, materials science, and (co)crystal engineering for their ability to produce a range of materials,[1] and such methods have been applied to the preparation of molecular semiconductors,[2] pharmaceuticals,[3] and optical materials.[4] The method involves a reaction between several solid reactants or between solid and liquid reactants by grinding in the absence of a solvent, and this aspect has inspired the development of ever-more efficient and versatile mechanochemical methodologies.[5–7]

The Diels–Alder reaction is one of the most significant and widely used protocols for carbon–carbon, carbon–heteroatom, or heteroatom–heteroatom bond-forming reactions to produce cyclic compounds in synthetic organic chemistry,[8] and is widely employed for the synthesis of natural products, pharmaceutically important molecules, and related compounds.[9–11] The most common methods to accelerate such reactions involve the use of various Lewis acid catalysts in solvents such as THF, toluene, or ionic liquids, or performing the reaction at elevated temperatures.[12–22]

Reports on solvent-free Diels–Alder reactions have appeared sporadically in the literature.[22] For example, Huertas and co-workers reported neat Diels–Alder reactions,[23] but almost all examples suffered from very low to low yields of the corresponding products and required elevated temperatures. Zang et al. described a reaction between cyclopentadiene and various *N*-arylmaleimides in a ball-mill apparatus;[24] however, when they attempted to simplify the methodology by carrying out the reaction of cyclopentadiene with *N*-tosylmaleimide through hand grinding, they obtained only a 54% yield of the product.

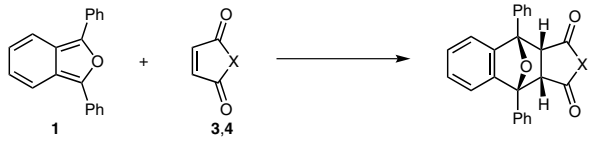
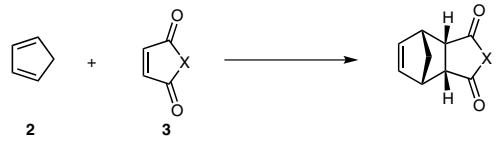
In continuation of our efforts on green approaches in organic synthesis,[25,26] we report a practical and operationally simple method for performing Diels–Alder reactions that involves manual grinding of two reactants in a pestle and mortar without a catalyst at ambient temperature; moreover, the method requires no purification steps. In some cases, we compared neat grinding with liquid-assisted grinding (LAG) in terms of yield and reaction time.

As a model reactant, we chose 1,3-diphenyl-2-benzofuran (**1**) as the diene because the new double bond of the Diels–Alder adduct would be part of the aromatic ring, making the reaction irreversible. Consequently, the cycloaddition reaction of benzofuran **1** with *N*-phenylmaleimide (**3a**) as the dienophile was tested by using both neat grinding and liquid-assisted grinding techniques (Scheme 1). Initially, the reaction was performed by mixing equimolar amounts of the two solid reactants in a pestle and mortar, and then grinding vigorously without using any additional liquid (Method A).[27] Although the reaction went to completion in 15 minutes, manual grinding required a good deal of effort (Table 1, entry 1). When the reaction mixture was wetted with 2–3 drops of ethyl acetate, the reaction was complete within two minutes, and it gave the corresponding tetracyclic product **5a** in quantitative yield (Method B)[28] (entry 2). Therefore, the LAG methodology accelerated the reaction and, most significantly, the purity of the product was good enough to permit spectroscopic analysis.




**Scheme 1** Diels–Alder reactions of 1,3-diphenyl-2-benzofuran or cyclopentadiene with various *N*-arylmaleimides

**Table 1** Diels–Alder Reactions of 1,3-Diphenyl-2-benzofuran or Cyclopentadiene with Various Dienophiles

| Entry | Dienophile | X | Cycloadduct | Method[a] | Time (min) | Yield[b] (%) |
|---|---|---|---|---|---|---|
| |  | | | | | |
| 1 | **3a** | NPh | **5a** | A | 15 | 98 |
| 2 | | | | B | 1 | quant |
| 3 | **3b** | N($C_6H_4$-4-Br) | **5b** | A | 20 | 95 |
| 4 | | | | B | 2 | quant |
| 5 | **3c** | N($C_6H_4$-4-Cl) | **5c** | A | 20 | 94 |
| 6 | | | | B | 2 | quant |
| 7 | **3d** | N($C_6H_4$-4-OMe) | **5d** | A | 30 | 75 |
| 8 | | | | B | 5 | quant |
| 9 | **3e** | NBn | **5e** | A | 25 | quant |
| 10 | | | | B | 2 | quant |
| 11 | **4** | O | **6** | A | 30 | 90 |
| 12 | | | | B | 2 | quant |
| |  | | | | | |
| 13 | **3a** | NPh | **7a** | A | 1 | quant |
| 14 | **3b** | N($C_6H_4$-4-Br) | **7b** | A | 3 | quant |
| 15 | **3c** | N($C_6H_4$-4-Cl) | **7c** | A | 3 | quant |
| 16 | **3d** | N($C_6H_4$-4-OMe) | **7d** | A | 5 | quant |
| 17 | **3e** | NBn | **7e** | A | 2 | quant |

[a] *Method A*: The reaction was carried out by grinding the two reactants (1 mmol each) for the time shown in the table. *Method B*: The reaction was carried out by grinding the two reactants (1 mmol each) in the presence of 2–3 drops of EtOAc for the time shown in the table.
[b] Yield of pure isolated product.

Encouraged by these results, we tested the reactions of other *N*-substituted maleimides **3b–e** with benzofuran **1** using both protocols. Although all the reactions gave the corresponding products **5b–e** in quantitative yields, the rate of the reaction was affected by the substituents on the arene moiety of the maleimide derivative (Table 1, entries 3–10). For example, the reaction of *N*-(4-methoxyphenyl)maleimide (**3d**) with benzofuran **1** did not reach completion after 30 minutes of neat grinding, and afforded the product in only 75% yield. However, by using the LAG protocol, complete conversion of the reactants was achieved in five minutes, giving product **5d** in quantitative yield. It is noteworthy that the success of such protocols relies on the fact that the reactants are consumed completely to afford the desired products; the presence of even small amounts of unreacted starting materials or byproducts would result in the need for purification steps. Consequently, in almost all the above examples, the LAG protocol was found to be optimal for achieving complete conversion of the reactants. Another observation was that the progress of each of the reactions of diene **1** with dienophiles **3a–e** could be followed visually, because the initially yellow-colored reaction mixture was transformed into a white product on completion of the reaction.

The reaction of **1** with maleic anhydride (**4**) with neat grinding provided adduct **6** in 90% yield in 30 minutes (Table 1, entry 11). However, when this reaction was performed by using the LAG protocol (Method B), it proceeded smoothly to give **6** in quantitative yield in only two minutes (entry 12).

We next chose cyclopenta-1,3-diene (**2**) as the diene. Freshly distilled cyclopenta-1,3-diene was added to the solid yellow imide **3a** in a mortar, and the resulting mixture was ground for one to two minutes. During this period, the initially pasty yellow reaction mixture became a white solid, indicating complete conversion of the reactants into the tricyclic Diels–Alder adduct **7a**, which was obtained in quantitative yield (Table 1, entry 13). No cyclopentadiene dimer or any other byproduct was formed. The resultant product was pure enough for standard spectroscopic analysis.

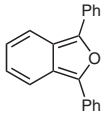
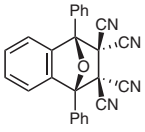
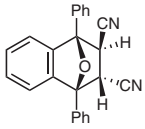
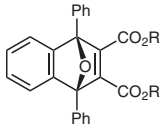
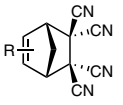
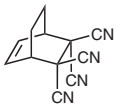
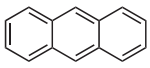
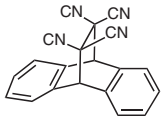
These results encouraged us to study the reactions of other *N*-phenylmaleimide derivatives **3b–d** and **3e** with cyclopentadiene **2** by using the same hand-grinding method. Gratifyingly, all the reactions furnished the corresponding product **7b–e** in quantitative yield within minutes (Table 1, entries 14–16). As before, the rate of the reaction was affected by the substituents on the arene moiety of the ma-

leimide; for instance, the reaction between diene **2** and *N*-(4-methoxyphenyl)maleimide (**3d**) required five minutes of grinding for complete conversion of reactants into the adduct **7d**, whereas the reaction of 4-halo-substituted *N*-arylmaleimides **3b** and **3c** took less time to give the corresponding adducts **7b** and **7c** in quantitative yield.

To test further the generality of this methodology, we then extended our Diels–Alder protocol to various dienes and dienophiles. Nitrile group containing dienophiles, such as tetracyanoethylene (**11**) and fumaronitrile (**12**), were tested with diene **1**. Gratifyingly, these reactions also reached completion rapidly to afford the tricyclic products **15** and **16**, respectively (Table 2, entries 1 and 2). Furthermore, when 1,3-diphenyl-2-benzofuran (**1a**) was treated with a stoichiometric amount of a dialkyl acetylenedicarboxylate **13** or **14**, the green-colored reaction mixture was transformed into a white solid within minutes to provide the pure product **17** or **18**, respectively, in quantitative yield (entries 3 and 4). The reaction of cyclopentadiene (**2**) or methylcyclopentadiene (**8**) with the highly electron-deficient dienophile tetracyanoethylene (**11**) was complete within one minute and gave the bicyclic product **19** or **20**, respectively, in quantitative yield (entries 5 and 6). The reactions of less-reactive dienes such as cyclohexa-1,3-diene (**9**) or anthracene **10** with tetracyanoethylene (**11**) successfully also gave the corresponding Diels–Alder products **21** and **22**, respectively, in quantitative yield within minutes (entries 7 and 8). However, when we attempted the cycloaddition reaction of cyclopentadiene with alkynedioates **13** and **14**, disappointingly, no reaction was observed.

In conclusion, a very simple, highly efficient, catalyst-free approach has been developed for promoting the Diels–Alder reaction of various dienes with dienophiles. The method provides the products within minutes in near-quantitative yields and without the formation of any by-products.

**Table 2** Diels–Alder Reactions of Various Dienes and Electron-Deficient Dienophiles under Green Conditions

| Entry | Diene | Dienophile | Cycloadduct | Method[a] | Time (min) | Yield[a] (%) |
|---|---|---|---|---|---|---|
| 1 |  **1** |  **11** |  **15** | B | 1 | quant |
| 2 | **1** |  **12** |  **16** | B | 4 | quant[c] |
| 3<br>4 | **1** |  **13**, R = Me<br>**14**, R = Et |  **17**, R = Me<br>**18**, R = Et | A<br>A | 2<br>2 | quant<br>quant |
| 5<br>6 |  **2**, R = H<br>**8**, R = Me |  **11** |  **19**, R = H<br>**20**, R = Me | A<br>A | 1<br>1 | quant<br>quant |
| 7 |  **9** |  **11** |  **21** | A | 3 | quant |
| 8 |  **10** |  **11** |  **22** | A | 2 | quant |

[a] *Method A*: The reaction was carried out by grinding the two reactants (1 mmol each) for the time shown in the table. *Method B*: The reaction was carried out by grinding the two reactants (1 mmol each) in the presence of 2–3 drops of EtOAc for the time shown in the table.
[b] Yield of pure isolated product.
[c] Combined yield of a 1:1 mixture of diastereomers. The structure of only one diastereomer is shown.

## Acknowledgements

J.A. thanks UGC, New Delhi, and R.R. thanks MHRD for the awards of their research fellowships.

## Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0036-1558970.

## References and notes

(1) For selected reviews and papers, see: (a) Friščić, T.; Jones, W. *Cryst. Growth Des.* **2009**, *9*, 1621. (b) Friščić, T. *J. Mater. Chem.* **2010**, *20*, 7599. (c) Braga, D.; D'Addario, D.; Giaffreda, S. L.; Maini, L.; Polito, M.; Grepioni, F. *Top. Curr. Chem.* **2005**, *254*, 71. (d) Boldyrev, V. V.; Tkáčová, K. *J. Mater. Synth. Process.* **2000**, *8*, 121. (e) Wang, G.-W. *Chem. Soc. Rev.* **2013**, *42*, 7668. (f) James, S. L.; Adams, C. J.; Bolm, C.; Braga, D.; Collier, P.; Friščić, T.; Grepioni, F.; Harris, K. D. M.; Hyett, G.; Jones, W.; Krebs, A.; Mack, J.; Maini, L.; Orpen, A. G.; Parkin, I. P.; Shearouse, W. C.; Steed, J. W.; Waddell, D. C. *Chem. Soc. Rev.* **2012**, *41*, 413. (g) Tanaka, S.; Kida, K.; Nagaoka, T.; Ota, T.; Miyake, Y. *Chem. Commun.* **2013**, *49*, 7884. (h) Harris, K. D. M. *Nat. Chem.* **2013**, *5*, 12. (i) Zhu, S.-E.; Li, F.; Wang, G.-W. *Chem. Soc. Rev.* **2013**, *42*, 7535. (j) Biswal, B. P.; Chandra, S.; Kandambeth, S.; Lukose, B.; Heine, T.; Banerjee, R. *J. Am. Chem. Soc.* **2013**, *135*, 5328. (k) Dou, H.; Nie, P.; MacFarlane, D. R. *J. Mater. Chem. A* **2014**, *2*, 19536. (l) Klimakow, M.; Klobes, P.; Thünemann, A. F.; Rademann, K.; Emmerling, F. *Chem. Mater.* **2010**, *22*, 5216. (m) Gorrasi, G.; Sorrentino, A. *Green Chem.* **2015**, *17*, 2610.

(2) (a) Jones, W.; Motherwell, W. D. S.; Trask, A. V. *MRS Bull.* **2006**, *31*, 875. (b) Trask, A. V.; Motherwell, W. D. S.; Jones, W. *Cryst. Growth Des.* **2005**, *5*, 1013. (c) Trask, A. V.; Motherwell, W. D. S.; Jones, W. *Int. J. Pharm. (Amsterdam, Neth.)* **2006**, *320*, 114. (d) Aakeröy, C. B.; Fasulo, M. E.; Desper, J. *Mol. Pharmaceutics* **2007**, *4*, 317. (e) Rodríguez-Hornedo, N. *Mol. Pharmaceutics* **2007**, *4*, 299. (f) Childs, S. L.; Chyall, L. J.; Dunlap, J. T.; Smolenskaya, V. N.; Stahly, B. C.; Stahly, G. P. *J. Am. Chem. Soc.* **2004**, *126*, 13335.

(3) Sokolov, N.; Friščić, T.; MacGillivray, L. R. *J. Am. Chem. Soc.* **2006**, *128*, 2806.

(4) (a) Etter, M. C.; Frankenbach, G. M.; Adsmond, D. A. *Mol. Cryst. Liq. Cryst.* **1990**, *187*, 25. (b) Smolka, T.; Sustmann, R.; Boese, R. *J. Prakt. Chem.* **1999**, *341*, 378. (c) Morimoto, M.; Kobatake, S.; Irie, M. *Chem. Commun.* **2008**, 335.

(5) (a) Baird, C. *Environmental Chemistry*; W. H. Freeman: New York, **1999**, 2nd ed.. (b) *Green Chemical Syntheses and Processes, ACS Symposium Series 767*; Anastas, P.; Heine, L. G.; Williamson, T. C., Eds.; American Chemical Society: Washington DC, **2000**. (c) Matlack, A. S. *Introduction to Green Chemistry*; Marcel Dekker: New York, **2001**. (d) Lancaster, M. *Green Chemistry: An Introductory Text*; Royal Society of Chemistry: Cambridge, **2002**.

(6) (a) Anastas, P. T.; Warner, J. C. *Green Chemistry: Theory and Practice*; Oxford University Press: Oxford, **1998**. (b) Lancaster, M. In *Handbook of Green Chemistry and Technology*; Clark, J. H.; Macquarrie, D. J., Eds.; Blackwell Science: Oxford, **2002**, Chap. 2, 10. (c) Bruckmann, A.; Krebs, A.; Bolm, C. *Green Chem.* **2008**, *10*, 1131. (d) Horváth, I. T. *Green Chem.* **2008**, *10*, 1024. (e) *Handbook of Green Chemistry*; Crabtree, R. H.; Anastas, P. T., Eds.; Wiley-VCH: Weinheim, **2009**.

(7) (a) Tanaka, K. *Solvent-Free Organic Synthesis*; Wiley-VCH: Weinheim, **2009**. (b) Marvaniya, H. M.; Modi, K. N.; Sen, D. J. *Int. J. Drug Develop. Res.* **2011**, *3*, 34.

(8) (a) Fringuelli, F.; Taticchi, A. *The Diels–Alder Reaction: Selected Practical Methods*; Wiley: Chichester, **2009**. (b) *Cycloaddition Reactions in Organic Synthesis*; Kobayashi, S.; Jørgensen, K. A., Eds.; Wiley-VCH: Weinheim, **2002**.

(9) (a) Takao, K.; Munakata, R.; Tadano, K.-i. *Chem. Rev.* **2005**, *105*, 4779. (b) Samarakoon, T.; Hanson, P. R. *Chemtracts* **2007**, *20*, 220. (c) Juhl, M.; Tanner, D. *Chem. Soc. Rev.* **2009**, *38*, 2983.

(10) (a) Abdelkafi, H.; Evanno, L.; Deville, A.; Dubost, L.; Chiaroni, A.; Nay, B. *Eur. J. Org. Chem.* **2011**, 2789. (b) Bautista, R.; Bernal, P.; Montiel, L. E.; Tamariz, J. *Synthesis* **2011**, 929.

(11) (a) de Mier-Vinué, J.; Gay, M.; Montaña, Á. M.; Sáez, R.-I.; Moreno, V.; Kasparkova, J.; Vrana, O.; Heringova, P.; Brabec, V.; Boccarelli, A.; Coluccia, M.; Natile, G. *J. Med. Chem.* **2008**, *51*, 424. (b) Lu, H.-H.; Pronin, S. V.; Koch, Y. A.; Meister, S.; Winzeler, E. A.; Shenvi, R. A. *J. Am. Chem. Soc.* **2016**, *138*, 7268. (c) Pronin, S. V.; Shenvi, R. A. *J. Am. Chem. Soc.* **2012**, *134*, 19604. (d) Wan, C. Y.; Deng, J.; Liu, H.; Bian, M.; Li, A. *Sci. Chin.: Chem.* **2014**, *57*, 926. (e) Dhambri, S.; Mohammad, S.; Van Buu, O. N.; Galvani, G.; Meyer, Y.; Lannou, M.-I.; Sorin, G.; Ardisson, J. *Nat. Prod. Rep.* **2015**, *32*, 841. (f) El-Desoky, A. H.; Kato, H.; Kagiyama, I.; Hitora, Y.; Losung, F.; Mangindaan, R. E. P.; de Voogd, N. J.; Tsukamoto, S. *J. Nat. Prod.* **2017**, *80*, 90. (g) Iovine, V.; Benni, I.; Sabia, R.; D'Acquarica, I.; Fabrizi, G.; Botta, B.; Calcaterra, A. *J. Nat. Prod.* **2016**, *79*, 2495.

(12) Silvero, G.; Arévalo, M. J.; Bravo, J. L.; Ávalos, M.; Jiménez, J. L.; López, I. *Tetrahedron* **2005**, *61*, 7105.

(13) López, I.; Silvero, G.; Arévalo, M. J.; Babiano, R.; Palacios, J. C.; Bravo, J. L. *Tetrahedron* **2007**, *63*, 2901.

(14) Ogasawara, Y.; Uchida, S.; Yamaguchi, K.; Mizuno, N. *Chem. Eur. J.* **2009**, *15*, 4343.

(15) Berson, J. A. *J. Am. Chem. Soc.* **1953**, *75*, 1240.

(16) Cava, M. P.; McGrady, J. *J. Org. Chem.* **1975**, *40*, 72.

(17) Naito, K.; Rickborn, B. *J. Org. Chem.* **1980**, *45*, 4061.

(18) Tsurusaki, T.; Sasamori, N.; Tokitoh, N. *Organometallics* **2009**, *28*, 3604.

(19) Middleton, W. J.; Heckert, E.; Little, E. L.; Krespan, C. G. *J. Am. Chem. Soc.* **1958**, *80*, 2783.

(20) Harjani, J. R.; Singer, R. D.; Garcia, M. T.; Scammells, P. J. *Green Chem.* **2009**, *11*, 83.

(21) Goldschmidt, Z.; Genizi, E. *Tetrahedron Lett.* **1987**, *28*, 4867.

(22) (a) Kim, J. H.; Hubig, S. M.; Lindeman, S. V.; Kochi, J. K. *J. Am. Chem. Soc.* **2001**, *123*, 87. (b) Kishan, K. V. R.; Desiraju, G. R. *J. Org. Chem.* **1987**, *52*, 4640. (c) Kim, J. H.; Lindeman, S. V.; Kochi, J. K. *J. Am. Chem. Soc.* **2001**, *123*, 4951. (d) Murata, Y.; Kato, N.; Fujiwara, K.; Komatsu, K. *J. Org. Chem.* **1999**, *64*, 3483.

(23) Huertas, D.; Florscher, M.; Dragojlovic, V. *Green Chem.* **2009**, *11*, 91.

(24) Zhang, Z.; Peng, Z.-W.; Hao, M.-F.; Gao, J.-G. *Synlett* **2010**, 2895.

(25) Choudhary, G.; Peddinti, R. K. *Green Chem.* **2011**, *13*, 276.

(26) Choudhary, G.; Peddinti, R. K. *Green Chem.* **2011**, *13*, 3290.

(27) **Method A: Solid–Liquid or Solid–Solid Reactant Combinations; General Procedure**
A mixture of the diene (1 mmol) and the dienophile (1 mmol) was subjected to hand grinding with a pestle and mortar for the time shown in Tables 1 and 2 to afford the corresponding products in quantitative yield. In the reactions of cyclopentadiene, 1.2 equiv of the diene was used. In most cases, product formation was observed by the change in color; with aryl maleimides, the yellow color of the initial reaction mixture changed to white, whereas with 1,3-diphenyl-2-benzofuran, the color of

the mixture changed almost immediately from fluorescent green to white.

**2-(4-Bromophenyl)-3a,4,7,7a-tetrahydro-1*H*-4,7-methanoisoindole-1,3-dione (7b)**

White solid; yield: 317 mg (quant); mp 156 °C. $^1$H NMR (500 MHz, $CDCl_3$): δ = 7.55 (dt, *J* = 2.5, 9.0 Hz, 2 H), 7.04 (dt, *J* = 2.5, 9.5 Hz, 2 H), 6.25 (t, *J* = 1.5 Hz, 2 H), 3.53–3.47 (m, 2 H), 3.43 (q, *J* = 1.5 Hz, 2 H), 1.79 (d, *J* = 9.0 Hz, 1 H), 1.61 (d, *J* = 9.0 Hz, 1 H). $^{13}$C NMR (125 MHz, $CDCl_3$): δ = 176.3, 134.5, 132.1, 130.7, 128.1, 122.2, 52.1, 45.7, 45.4.

**2-(4-Methoxyphenyl)-3a,4,7,7a-tetrahydro-1*H*-4,7-methanoisoindole-1,3-dione (7d)**

White solid; yield: 170 mg (quant); mp 269 °C. $^1$H NMR (500 MHz, $CDCl_3$): δ = 7.04 (d, *J* = 8.0 Hz, 2 H), 6.93 (d, *J* = 8.0 Hz, 2 H), 6.25 (s, 2 H), 3.80 (s, 3 H), 3.50 (s, 2 H), 3.41 (s, 2 H), 1.78 (d, *J* = 8.5 Hz, 1 H), 1.60 (d, *J* = 8.0 Hz, 1 H). $^{13}$C NMR (125 MHz, $CDCl_3$): δ = 177.1, 159.4, 134.5, 127.8, 124.4, 114.4, 55.4, 52.2, 45.6, 45.4.

**Diethyl 1,4-Diphenyl-1,4-dihydro-1,4-epoxynaphthalene-2,3-dicarboxylate (18)**

White solid; yield: 440 mg (quant); mp 115 °C. $^1$H NMR (500 MHz, $CDCl_3$): δ = 7.79 (d, *J* = 7.0 Hz, 4 H), 7.56 (dd, *J* = 3.0, 5.0 Hz, 2 H), 7.52–7.43 (m, 6 H), 7.18 (dd, *J* = 3.0, 5.0 Hz, 2 H), 4.23–4.12 (m, 4 H), 1.17 (t, *J* = 7.0 Hz, 6 H). $^{13}$C NMR (125 MHz, $CDCl_3$): δ = 163.6, 153.7, 149.2, 133.2, 129.0, 128.4, 128.1, 125.9, 122.1, 94.0, 61.3, 13.8.

**Bicyclo[2.2.1]hept-5-ene-2,2,3,3-tetracarbonitrile (19)**

White solid; yield: 194 mg (quant); mp 217 °C. $^1$H NMR (500 MHz, $CDCl_3$): δ = 6.52 (s, 2 H), 4.06 (s, 2 H), 2.25 (s, 2 H). $^{13}$C NMR (125 MHz, $CDCl_3$): δ = 133.6, 111.9, 111.7, 110.9, 110.4, 107.9, 55.9, 46.7, 46.4.

**Bicyclo[2.2.2]oct-5-ene-2,2,3,3-tetracarbonitrile (21)**

White solid; yield: 208 mg (quant). $^1$H NMR (500 MHz, $CDCl_3$): δ = 6.69 (s, 2 H), 3.55 (s, 2 H), 2.24 (d, *J* = 9.5 Hz, 2 H), 1.62 (d, *J* = 9.5 Hz, 2 H). $^{13}$C NMR (125 MHz, $CDCl_3$): δ = 133.1, 111.7, 111.3, 107.9, 42.8, 39.1, 18.8.

(28) **Method B: Liquid-Assisted Grinding; General Procedure**

A mixture of the appropriate diene (1 mmol), dienophile (1 mmol), and EtOAc (2–3 drops) was subjected to hand grinding with a pestle in a mortar for the time shown in Tables 1 and 2. Almost immediately, the color of the mixture changed from fluorescent-green or yellow to white. The EtOAc was removed under vacuum to afford the pure solid product in quantitative yield.

**2-(4-Bromophenyl)-4,9-diphenyl-3a,4,9,9a-tetrahydro-1*H*-4,9-epoxybenzo[*f*]isoindole-1,3-dione (5b**)

White solid; yield: 521 mg (quant); mp 242 °C. $^1$H NMR (500 MHz, $CDCl_3$): δ = 8.05 (d, *J* = 7.5 Hz, 4 H), 7.54 (t, *J* = 7.5 Hz, 4 H), 7.47 (d, *J* = 7.0 Hz, 2 H), 7.28–7.22 (m, 4 H), 7.05 (dd, *J* = 3.0, 5.0 Hz, 2 H), 6.43 (d, *J* = 8.5 Hz, 2 H), 4.26 (s, 2 H). $^{13}$C NMR (125 MHz, $CDCl_3$): δ = 173.0, 144.0, 136.2, 132.1, 130.1, 128.8, 128.7, 128.3, 127.9, 127.1, 122.7, 120.8, 90.6, 54.3.

**2-(4-Methoxyphenyl)-4,9-diphenyl-3a,4,9,9a-tetrahydro-1*H*-4,9-epoxybenzo[*f*]isoindole-1,3-dione (5d)**

White solid; yield: 473 mg (quant); mp 209 °C. $^1$H NMR (500 MHz, $CDCl_3$): δ = 8.07 (d, *J* = 8.0 Hz, 4 H), 7.53 (t, *J* = 7.5 Hz, 4 H), 7.46 (t, *J* = 7.0 Hz, 2 H), 7.29–7.22 (m, 2 H), 7.06 (dd, *J* = 3.0, 5.0 Hz, 2 H), 6.79 (d, *J* = 8.5 Hz, 2 H), 6.42 (d, *J* = 9.0 Hz, 2 H), 4.24 (s, 2 H), 3.75 (s, 3 H). $^{13}$C NMR (125 MHz, $CDCl_3$): δ = 173.5, 159.5, 144.1, 136.3, 128.6, 128.5, 128.1, 127.5, 127.1, 123.7, 120.8, 114.2, 90.5, 55.3, 54.2.

**1,4-Diphenyl-1,2,3,4-tetrahydro-1,4-epoxynaphthalene-2,3-dicarbonitrile (16)**

White solid; yield: 378 mg (quant). $^1$H NMR (500 MHz, $CDCl_3$): δ = 7.84–7.79 (m, 2 H), 7.69–7.62 (m, 2 H), 7.60–7.59 (m, 6 H), 7.32–7.29 (m, 3 H), 7.15 (d, *J* = 7.0 Hz, 1 H), 3.87 (d, *J* = 4.5 Hz, 1 H), 3.54 (d, *J* = 4.0 Hz, 1 H). $^{13}$C NMR (125 MHz, $CDCl_3$): δ = 144.1, 142.8, 134.1, 133.3, 129.6, 129.2, 129.1, 129.0, 125.8, 125.5, 121.8, 119.7, 117.1, 117.0, 90.7, 44.4, 43.0.