Expeditious 'On-Water' Cycloaddition between N-Substituted Maleimides and Furans

María Victoria Gil, Verónica Luque-Agudo, Emilio Román,* José Antonio Serrano

Departamento de Química Orgánica e Inorgánica, Facultad de Ciencias, Universidad de Extremadura, Avda. de Elvas, s/n, 06071 Badajoz, Spain
Fax +34(924)271149; E-mail: roman@unex.es

Received: 23.05.2014; Accepted after revision: 04.07.2014

Abstract: Cycloaddition reactions between *N*-alkyl and *N*-aryl-substituted maleimides and furan derivatives have been carried out using the 'on-water' methodology. Transformations are faster and products can easily be isolated by simple workup protocols, often in quantitative yields.

Key words: cycloaddition, heterocycles, green chemistry

Synthetic organic chemistry is currently experiencing numerous innovations to develop environmentally friendly procedures that avoid the use of toxic or hazardous reagents, leading to safer and more efficient protocols. This so-called 'green chemistry' takes into account economic and ecological considerations, such as energy consumption, atom efficiency, and sustainability of chemical processes.[1] In this context, considerable research is devoted to alternative reaction media, such as solvent-free conditions, ionic liquids, or water, to reduce or eliminate the use of traditional organic solvents and the processing thereof. Among these options, the use of water as the supporting medium for a reaction opens up new and advantageous ways to perform organic transformations. By using this methodology, there have been in the last decades numerous reactions which not only have shown remarkable increases in both rates and yields when compared with the same processes in common organic solvents, but also they were more chemo-, regio-, and enantioselective; thus increasing the importance of those reactions performed in aqueous media.[2]

Sharpless et al.[3] coined the term 'on-water' reactions for those processes involving water-insoluble reactants in which a vigorous stirring of the reaction medium generates aqueous emulsions or suspensions in the absence of organic cosolvents. From an environmental point of view, this methodology where water plays the roles of reaction medium and catalyst is one of the most recent and promising innovations in organic synthesis.[4]

Literature reports about organic reactions that occur 'on water' are rapidly growing in number and this area has been reviewed.[5] Pericyclic reactions, such as Diels–Alder cycloadditions, are among the most frequently cited, probably because these processes were the first for which substantial changes in selectivities and accelerations were described on moving from organic solvents to aqueous conditions.[6,7]

The Diels–Alder cycloaddition plays a key role in syntheses of cantharidin (**1**) and norcantharidin (**2**, Figure 1), as well as some of their derivatives; those two compounds have similar biological activity, the former being the most effective ingredient in the preparation of several healing products used in ancient Chinese medicine and against certain malignant tumors worldwide. Some derivatives of *exo*-5,6-dehydronorcantharidin (**3**) also exhibit pharmacological activity.[8] Currently, the use of these compounds in clinical practice is replacing cantharidin due to their lower toxicity and greater ease of synthesis.[9]

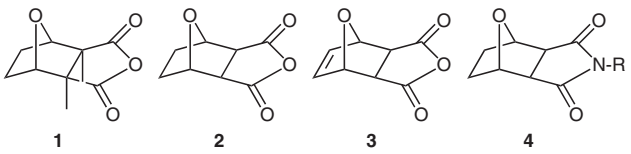
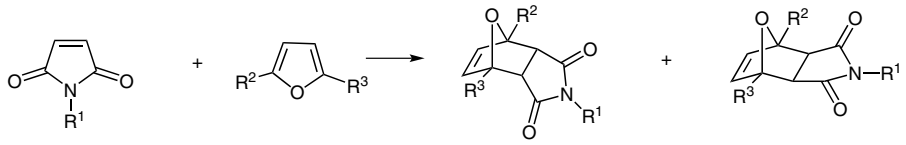


Figure 1 Pharmacologically active cantharidin (**1**) and related products

The unsaturated oxabicycle **3** is the immediate precursor, via **2**, of a series of norcantharimides **4**, which have shown moderate to good cytotoxicity in anticancer evaluation,[10] as well as good antiplasmodial activity.[11] The presence of the imide moiety is a structural requisite for several important bioactive molecules showing antitumor, antiviral, analgesic, sedative, and fungicide properties.[9b,12] Herein we report highly efficient Diels–Alder reactions between furan derivatives and three maleimides, by using the environmentally benign 'on-water' protocol.

Reactions between *N*-phenyl-, *N*-ethyl-, and *N*-*tert*-butylmaleimides (**5a**–**c**) with furan, 2-methylfuran, and 2,5-dimethylfurans (**6a**–**c**) were carried out either at ambient temperature or at 65 °C. In all cases, the reagents were insoluble or only slightly soluble in water, forming an aqueous suspension after vigorous magnetic stirring. An excess of furan or derivatives were used to dissolve the solid maleimides **5a** and **5b**, whereas stoichiometric amounts of the same furans were employed with liquid maleimide **5c**. Under both temperature conditions, *N*-phenyl- and *N*-ethylmaleimides (**5a** and **5b**) afforded mixtures of the corresponding *endo*- and *exo*-Diels–Alder adducts **7**–**12** (Scheme 1 and Table 1) in quantitative yields, although for **5c**, the yields are of product obtained after achieving equilibrium at 25 °C. With the exception

SYNLETT 2014, 25, 2179–2183
Advanced online publication: 13.08.2014
DOI: 10.1055/s-0034-1378560; Art ID: st-2014-d0448-l



5a, R^1 = Ph
5b, R^1 = Et
5c, R^1 = *t*-Bu

6a, $R^2 = R^3$ = H
6b, R^2 = H, R^3 = Me
6c, $R^2 = R^3$ = Me

	R^1	R^2	R^3	
7a	Ph	H	H	**7b**
8a	Ph	H	Me	**8b**
9a	Ph	Me	Me	**9b**
10a	Et	H	H	**10b**
11a	Et	H	Me	**11b**
12a	Et	Me	Me	**12b**
13a	*t*-Bu	H	H	**13b**
14a	*t*-Bu	H	Me	**14b**
15a	*t*-Bu	Me	Me	**15b**

Scheme 1

of the cycloaddition between **5c** and **9**, reaction times were shorter at 65 °C.

Table 1 Diels–Alder Reactions between Furans **6a–c**, **9** and Maleimides **5a–c**[29]

Imide	Diene	Time (h)[a,b]	Yield (%)[a,b]	Product(s)	Ratio *endo*/*exo*
5a	**6a**	3.0[a]	quant.[a,b]	**7a**/**7b**[24]	1.6:1[a]
	6b	1.5[b]	quant.[a,b]	**8a**/**8b**	1.6:1[b]
	6c	0.6[a]	quant.[a,b]	**9a**/**9b**	1.3:1[a]
	9	0.3[b]	quant.[a,b]	**16a**[26]	0:1[b]
		1.0[a]			5:1[a]
		0.5[b]			1.2:1[b]
		1.5[a]			0:1[a]
		0.25[b]			0:1[b]
5b	**6a**	3.0[a]	quant.[a,b]	**10a**/**10b**	6:1[a]
	6b	1.0[b]	quant.[a,b]	**11a**/**11b**	1.4:1[b]
	6c	2.5[a]	quant.[a,b]	**12a**/**12b**	1.5:1[a]
	9	1.0[b]	quant.[a,b]	**19b**[27]	1:1.7[b]
		0.6[a]			6.5:1[a]
		0.25[b]			3.5:1[b]
		0.45[a]			
		0.25[b]			
5c	**6a**	51[a]	38[c]	**13a**/**13b**[25]	1:1.6[a]
	6b	26[b]	37[b]	**14a**/**14b**	0:1[b]
	6c	51[a]	61[c]	**15a**/**15b**	1:8[a]
	9	23[b]	56[c]	**20c**/**21c**[28]	0:1[b]
		1.3[a]	82[c]		2.3:1[a]
		1.0[b]	30[b]		1:2.5[b]
		0.6[a]	37[c]		2:1[a]
		1.0[b]	37[b]		0:1[b]

[a] Results from reactions at r.t.
[b] Results from reactions at 65 °C.
[c] Incomplete reactions: conversion rates are calculated when equilibrium is reached.

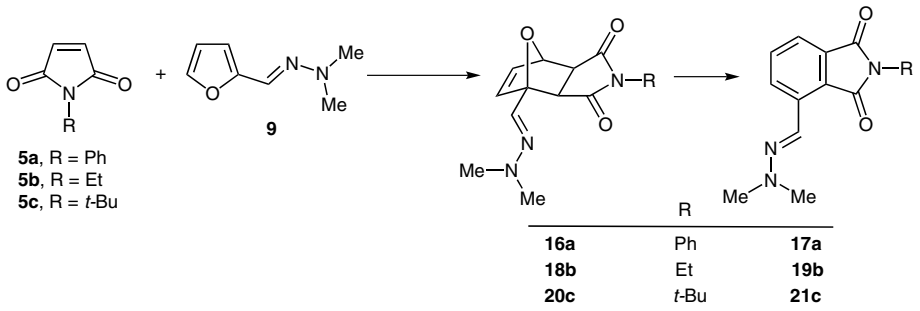
At 25 °C, the adducts from olefins **5a** or **5b** were predominantly *endo*, whereas an increase in *exo* adducts was observed when the cycloadditions were carried out at 65 °C. At this temperature, only the *exo* products **8b**, **13b**, and **14b** were formed in the cycloadditions of **5a** and **6b**, **5c** and **6a**, or **5c** and **6b**, respectively.

Compound *exo*-**11b** was prevalent in the mixture of **11a**/**11b**. This behavior could be explained by considering that the *exo* adducts are compounds of thermodynamic control. It should be noted that **7b** and **8b** were obtained quantitatively; thus, the former was resulting from heating the mixture of **7a** + **7b** at 95–100 °C, whereas the latter was obtained directly from the cycloaddition at 65 °C. The imide-oxabicycle **7b** has been used as starting material for the preparation of perhydroisoindoles showing broad pharmacological activity.[13] Adducts **7a**, **8a**, **9a**,**b, 10a**, **11b**, and **12a** were isolated in pure form by preparative thin-layer chromatography, having been used compounds **10a** and **10b** as monomers in the alternating copolymerization with cyclooctene, via ring-opening metathesis of copolymers with polar tailorable functionalities linked by nonpolar spacers.[14] Similarly, the treatment of furans **6a–c** with *N*-*tert*-butylmaleimide (**5c**) led to the corresponding cycloadducts as *endo–exo* mixtures, from which **13a**,**b**, **14b**, and **15a**,**b** could be isolated by PTLC.

The outcomes of the reaction between furfural *N*,*N*-dimethylhydrazone (**9**) and maleimides **5a–c** (Scheme 2 and Table 1) were different from those described above. Thus, either at room temperature or at 65 °C, the treatment of **9** with **5a** led quantitatively to the *exo* adduct **16a**, whereas with **5b** the phthalimide **19b** was exclusively obtained and, in the case of **5c**, the product consisted of a mixture of **20c** and **21c**.

Heating of an aqueous suspension of **16a** in water at 95–100 °C for 50 minutes gave phthalimide **17a** in 94% yield. The conversion of **18b** into **19b** proceeded spontaneously under the reaction conditions at 25 °C for 27 minutes or by heating either at 65 °C for 15 minutes.

Treatment of hydrazone **9** with *N*-*tert*-butylmaleimide (**5c**) yielded a 2:1 mixture of cycloadduct **20c** and phthalimide **21c** (Table 1); however, after stirring for six hours at room temperature, the ratio **20c**/**21c** became 1:6.1. When this reaction was performed at 65 °C, only phthalimide **21c** was obtained. We propose that the formation of phthalimides through ring opening of *exo*-7-oxabicycle followed by dehydration is aided by electron donation from the hydrazono substituent assisting in the rupture of the oxygen bridge;[15] however, no cycloadduct



Scheme 2 'On-water' cycloadditions between maleimides **5a**–**c** and furfural *N*,*N*-dimethylhydrazone (**9**)

18b could be detected by ^{1}H NMR analysis of the reaction mixture of **9** and **5b**.

It should be noted that the 'on-water' reaction between furfural *N*,*N*-dimethylhydrazone (**9**) and maleimide (**5a**) led quantitatively to *exo* adduct **16a**. The structure of the latter is of great interest either in itself or as immediate precursor of products with potential biological activity;[12] furthermore, phthalimides **17a**, **19b**, and **21c** are closely related to compounds which are useful for preventing or treating diseases or conditions related to an abnormally high level or activity of tumor necrosis factor α in mammals.[16]

In order to highlight the improvements we have achieved by using the 'on-water' methodology, a comparison follows between our results and those reported in previous syntheses for some of the products described herein or other with similar structures. Thus, the reaction between *N*-phenylmaleimide (**5a**) and furan **6a** has been described[17] by dissolving the maleimide in furan, without any additional organic solvent; the mixture was allowed to stand for at least 20 hours and, after ten days, crystallization of adducts **7a** and **7b** took place as a mixture that was filtered and washed with diethyl ether (88% yield, 36:64 respective ratio). The same reaction was conducted in solutions in diethyl ether, in benzene, or in $CDCl_3$; in the latter case, the process was monitored by ^{1}H NMR and gave 86% conversion after seven days at 0 °C, with an *exo–endo* ratio of 36:49; 89% conversion after seven days at room temperature, with an *exo–endo* ratio of 48:41 and 91% conversion after 20 days at room temperature, with an *exo–endo* ratio of 68:23 (equilibrium ratio). In addition,[18] the solventless reaction between **5a** and **6a** on K10 montmorillonite at 0 °C for 24 hours gave 85% of a 1.3:1 mixture of **7a** and **7b** and, when additional microwave irradiation was used, 80% of the same mixture of adducts was produced after 15 minutes (1.5:1 ratio). No pure products were isolated.

Products from reactions involving stoichiometric quantities of 2-substituted furans and *N*-propyl, *N*-isobutyl, *N*-phenyl, or *N*-*tert*-butylmaleimides have been used as model compounds for the preparation of polymers.[19] The processes were carried out at 55 °C for 24–48 hours, in chloroform, the products being purified by silica gel column chromatography.

The cycloaddition of **5a** and **6b** has been described at room temperature for 24 hours, in a 4:1 mixture of toluene–benzene, under 11 kbar pressure. The product was obtained in 85% yield, as a 1:1.6 mixture of **8a**/**8b**.[20]

The reaction of *N*-phenylmaleimide (**5a**) with 2,5-dimethylfuran (**6c**) occurred in 90 minutes at 0 °C on K10 montmorillonite and in the absence of organic solvents;[18] the product was obtained in 77% yield, as a 2.3:1 mixture of **9a** and **9b**. When microwave irradiation was used, the same mixture of adducts was produced quantitatively after 15 minutes (2.3:1 ratio). No pure products were isolated.

A recent patent reported[21] two Diels–Alder reactions of *N*-maleimide propionic acid and *N*-(2-hydroxyethyl)maleimide with 2,5-dimethylfuran, leading to 3.5:1 and 4:1 mixtures of *exo*/*endo* adducts **22b**/**22a** and **23b**/**23a**, respectively (Figure 2). In the first case, the yield was quantitative after stirring for six hours in acetonitrile at 60 °C; whereas in the second case no yield was reported, the reaction being carried out in the same solvent under argon at 65 °C overnight. All of the four adducts could be isolated in pure form.

	R^1	R^2	R^3	
22a	CH_2CH_2COOH	Me	Me	**22b**
23a	CH_2CH_2OH	Me	Me	**23b**
24a	Me	H	H	**24b**

Figure 2 Structures for cycloadducts **22a**–**24b**

The cycloaddition between *N*-methylmaleimide and furan has been described in refluxing benzene[22] for 15 hours, affording **24a** and **24b** as a mixture that crystallized from diethyl ether (96% yield, ratio 3:2). When the same process was carried out in tetrahydrofuran at room temperature for 48 hours, the *endo*-adduct **24a** was isolated in 61% yield by fractional crystallization from the mixture of the adducts.[23]

The reaction of *N*-ethylmaleimide (**5b**) with hydrazone **9** has been reported[15] under stirring for 16 hours in chloro-

form at room temperature, resulting in 90% of solid phthalimide **19b** after extraction with diethyl ether. No ^{1}H NMR signals were detected for a hypothetical adduct precursor of this compound. Analogues of **19b**, with (2,6-dioxopiperidin-3-yl) as a substituent on the imide nitrogen have synthesized in a two-step thermal reaction for eight hours with solvent and catalyst.[16]

In conclusion, the results described in this paper show that the use of the 'on-water' protocol clearly improves previously reported procedures in one or more of the following aspects: no organic solvent as the reaction medium or during workup is required; no catalyst is needed; reaction times are shorter; yields are higher; the protocol is safer and more energy economical; and reaction conditions are milder. Therefore, this protocol meets the requirements to be considered 'green chemistry'.

Acknowledgment

V. Luque-Agudo acknowledges financial support of this work by a grant from the Plan de Iniciación a la Investigación, Desarrollo Tecnológico e Innovación 2013 of the University of Extremadura.

Supporting Information for this article is available online at http://www.thieme-connect.com/products/ejournals/journal/10.1055/s-00000083.

References and Notes

(1) Gawande, M. B.; Bonifácio, V. D. B.; Luque, R.; Branco, P. S.; Varma, R. S. *Chem. Soc. Rev.* **2013**, *42*, 5522.
(2) (a) Lindström, U. M. *Chem. Rev.* **2002**, *102*, 2715. (b) Li, C.-J. *Chem. Rev.* **2005**, *105*, 3095. (c) Horváth, I. T. *Green Chem.* **2008**, *10*, 1024. (d) Candeias, N. R.; Branco, L. C.; Góis, P. M. P.; Alfonso, C. A. M.; Trindade, A. F. *Chem. Rev.* **2009**, *109*, 2703.
(3) Narayan, S.; Muldoon, J.; Finn, M. G.; Fokin, V. V.; Kolb, H. C.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **2005**, *44*, 3275.
(4) (a) Jung, Y.; Marcus, R. A. *J. Am. Chem. Soc.* **2007**, *129*, 5492. (b) Beattie, J. K.; McErlean, C. S. P.; Phippen, C. B. W. *Chem. Eur. J.* **2010**, *16*, 8972. (c) Mellouli, S.; Bousekkine, L.; Theberge, A. B.; Huck, W. T. S. *Angew. Chem. Int. Ed.* **2012**, *51*, 7981.
(5) (a) Chanda, A.; Fokin, V. V. *Chem. Rev.* **2009**, *109*, 725. (b) Butler, R. N.; Coyne, A. G. *Chem. Rev.* **2010**, *110*, 6302. (c) Simon, M. O.; Li, C.-J. *Chem. Soc. Rev.* **2012**, *41*, 1415.
(6) (a) Rideout, D. C.; Breslow, R. *J. Am. Chem. Soc.* **1980**, *102*, 7816. (b) Breslow, R.; Maitra, U.; Rideout, D. C. *Tetrahedron Lett.* **1983**, *24*, 1901. (c) Breslow, R. In *Structure and Reactivity in Aqueous Solution, ACS Symposium Series 568*; Cramer, C. J.; Truhlar, D. G., Eds.; American Chemical Society: Washington DC, **1994**, 291.
(7) Grieco, P. A.; Garner, P.; He, Z. *Tetrahedron Lett.* **1983**, *24*, 1987.
(8) Hart, M. E.; Chamberlin, A. R.; Walkom, C.; Sakoff, J. A.; McCluskey, A. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1969.
(9) (a) Deng, L.; Yongzhou, H. *J. Heterocycl. Chem.* **2007**, *44*, 597. (b) Deng, L.-P.; Liu, F.-M.; Wang, H.-Y. *J. Heterocycl. Chem.* **2005**, *42*, 13.
(10) Hill, T. A.; Stewart, S. G.; Ackland, S. P.; Gilbert, J.; Sauer, B.; Sakoff, J. S.; McCluskey, A. *Bioorg. Med. Chem.* **2007**, *15*, 6126.
(11) Bajsa, J.; McCluskey, A.; Gordon, C. P.; Stewart, S. G.; Hill, T. A.; Sahu, R.; Duke, S. O.; Tekwani, B. L. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 6688.
(12) Göksu, G.; Öcal, N.; Kaufmann, D. E. *Molecules* **2010**, *15*, 1302.
(13) Göksu, G.; Gül, M.; Öcal, N.; Kaufmann, D. E. *Tetrahedron Lett.* **2008**, *49*, 2685.
(14) Ilker, M. F.; Coughlin, E. B. *Macromolecules* **2002**, *35*, 54.
(15) Potts, K. T.; Walsh, E. B. *J. Org. Chem.* **1988**, *53*, 1199.
(16) Muller, G. W.; Saindane, M.; Ge, C.; Kothare, M. A.; Cameron, L. M.; Rogers, M. E. US 20080064876 A1, **2008**.
(17) Cooley, J. H.; Williams, R. V. *J. Chem. Educ.* **1997**, *74*, 582.
(18) Avalos, M.; Babiano, R.; Bravo, J. L.; Cintas, P.; Jiménez, J. L.; Palacios, J. C. *Tetrahedron Lett.* **1998**, *39*, 9301.
(19) Canadell, J.; Fischer, H.; De With, G.; Van Benthem, R. A. T. M. *J. Polym. Sci., Part A: Polym. Chem.* **2010**, *48*, 3456.
(20) Jarosz, S.; Mach, M.; Szewczyk, K.; Skóra, S.; Ciunik, Z. *Eur. J. Org. Chem.* **2001**, 2955.
(21) Grandas, A. N.; Sánchez, A.; Pedroso, E. US 20130158248 A1, **2013**.
(22) Anderson, W. K.; Miowsky, A. S. *J. Org. Chem.* **1985**, *50*, 5423.
(23) Goh, Y. W.; Pool, B. R.; White, J. M. *J. Org. Chem.* **2008**, *73*, 151.
(24) **General Procedure for Cycloadditions between *N*-Phenyl- or *N*-Ethylmaleimides 5a,b and Furans 6a–c**
A) In a 10 mL round-bottom flask the maleimide (ca. 0.5 g) was dissolved in the minimum quantity of furan **6a–c** (0.5–1.7 mL); H_2O (3 mL) was added, and the resulting mixture was subjected to vigorous magnetic vigorous at 25 °C. After the time specified in Table 1, ^{1}H NMR spectroscopic analysis and TLC (EtOAc–hexane, 1:1) revealed the absence of starting materials and appearance of the respective cycloadducts. The products either immediately precipitated, from the reaction medium or after overnight storage in the refrigerator, and were filtered and washed on the filter with cold H_2O. In the case of reaction between **5b** and **6b**, the reaction mixture was diluted with brine (5 mL), extracted with CH_2Cl_2 (3 × 5 mL), the combined extracts dried over $MgSO_4$, filtered, and evaporated to afford an oil that crystallized after 24 h into the freezer. Then, the solid was collected by filtration and washed on the filter with cold H_2O.
Yields were quantitative and, in all cases, analytically pure samples of each one of the adducts could be isolated by preparative TLC. The *exo* adduct **7b** was the only product obtained after refluxing an aqueous suspension of a mixture of **7a** and **7b** for 45 min.
B) Following the same procedure above, reactions were complete after stirring at 65 °C for times specified in Table 1. Then, the adducts, which precipitated in the reaction mixture, were filtered and collected as indicated above.
(25) **General Procedure for Cycloadditions between *N*-*tert*-Butylmaleimide 5c and Furans 6a–c**
In a 10 mL round-bottom flask, *N*-*tert*-butylmaleimide (**5c**, 0.2 mL, 1.38 mmol) was mixed with an equimolar quantity of the furans **6a–c** (0.10–0.15 mL), H_2O was added (3 mL), and the resulting suspension was subjected to magnetic vigorous stirring at 25 °C. After times specified in Table 1, ^{1}H NMR and TLC (EtOAc–hexane, 1:2) analyses showed no further progress of the reaction with the mixture still containing unreacted starting materials. Except for the reaction between **5c** and **6a**, the products precipitated and were collected by filtration and washed on the filter with cold H_2O. In this case, workup of the reaction mixture was the same as indicated in ref. 24. Adducts **13a** and **13b** were separated by preparative TLC.

(26) **1-[(*E*)-2,2-Dimethylhydrazono]-7-oxabicyclo[2.2.1]hept-5-ene-2,3-*exo*-dicarboxy-*N*-phenylimide (16a) and 4-[(*E*)-2,2-Dimethylhydrazono]-2-phenylisoindoline-1,3-dione (17a)**
Following the two methods A and B as described above, cycloaddition of *N*-phenylmaleimide (**5a**) and furfural *N*,*N*-dimethylhydrazone (**9**) led quantitatively to adduct **16a** as a yellow solid that was filtered and washed on the filter with cold H_2O. By refluxing a suspension of **16a** (0.85 g) in H_2O (25 mL) for 50 min, this compound was converted quantitatively into phenylisoindoline **17a**, isolated by filtration as an yellow-orange solid and recrystallized from EtOH.

(27) **4-[(*E*)-2,2-Dimethylhydrazono]-2-ethylisoindoline-1,3-dione (19b)**
Following methods A and B as described above, treatment of *N*-ethylmaleimide (**5b**, 0.4 g, 3.20 mmol) and furfural *N*,*N*-dimethyl hydrazone (**9**, 0.5 mL, 3.77 mmol) led quantitatively to ethylisoindoline **19b** as a solid that was filtered and washed on the filter with cold H_2O.

(28) **1-[(*E*)-2,2-Dimethylhydrazono]-7-oxabicyclo[2.2.1]hept-5-ene-2,3-*exo*-dicarboxy-*N*-*tert*-butylimide (20c) and 4-[(*E*)-2,2-Dimethylhydrazono]-2-*tert*-butylisoindoline-1,3-dione (21c)**
Following the general procedure above described for the reactions of furans with *N*-*tert*-butyl maleimide (5c), treatment of the latter compound (0.2 mL, 1.38 mmol) with furfural *N*,*N*-dimethylhydrazone (9, 0.185 mL, 1.39 mmol) led to an equilibrium mixture (see Table 1) from which 37% yield of the title compounds were isolated by filtration and washing on the filter with cold H_2O.

(29) For ^{1}H NMR and ^{13}C NMR spectra of all compounds see the Supporting Information.