ORGANIC
LETTERS

2003
Vol. 5, No. 16
2833−2836

Diels–Alder Reactions of Fused Pyran-2-ones with Maleimides: Efficient Syntheses of Benz[e]isoindoles and Related Systems[†]

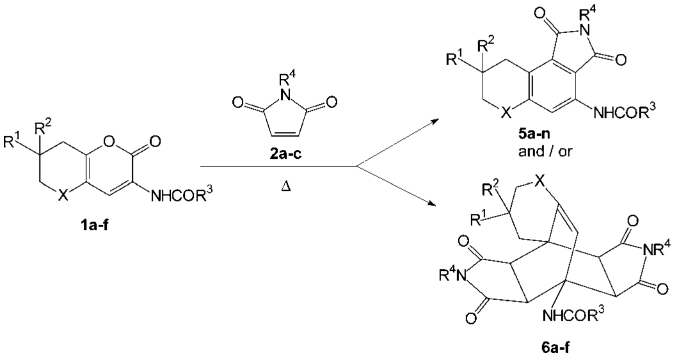
Krištof Kranjc, Slovenko Polanc, and Marijan Kočevar*

*University of Ljubljana, Faculty of Chemistry and Chemical Technology, Aškerčeva 5,
SI-1000 Ljubljana, Slovenia*

marijan.kocevar@uni-lj.si

Received May 16, 2003

ABSTRACT



The Diels–Alder reaction of some substituted 5,6,7,8-tetrahydro-2*H*-1-benzopyran-2-ones (1a–f) with N-substituted maleimides (2a–c) leading to fused isoindole derivatives (5a–n, 7) or, in a few cases, to bridged double cycloadducts (fused bicyclo[2.2.2]octene derivatives) (6a–f) is presented. When X = CO, the first efficient, substituent-driven aromatization of an intermediary-formed cycloadduct was observed, resulting in substituted benz[e]isoindoles (5a–k). The same type of aromatization can also be achieved in an unprecedented catalysis with Rh/C.

The Diels−Alder cycloaddition reaction, which is named after its discoverers,[1] is a very important synthetic tool. Starting from 2*H*-pyran-2-one derivatives, many interesting natural products and biologically important compounds have been prepared.[2] It has been shown that 2*H*-pyran-2-ones and fused pyran-2-ones react as dienes with alkynes to give aromatized fused systems after the extrusion of carbon dioxide.[3] On the other hand, for the case of alkenes, there are several possible reaction routes, yielding carbon dioxide-bridged compounds, new cyclodiene systems, aromatized systems, or double cycloadducts.[2] With the alkenes containing appropriate groups for an elimination (masked alkynes) or for a rearrangement, an aromatization occurs (after the elimination or rearrangement) and the products formed are

---

[†] Dedicated to Professor Sándor Antus, University of Debrecen, Hungary, on the occasion of his 60th birthday.

(1) (a) Diels, O.; Alder, K. *Justus Liebigs Ann. Chem.* **1926**, *450*, 237−254. (b) Diels, O.; Alder, K. *Justus Liebigs Ann. Chem.* **1927**, *460*, 98−122.

(2) (a) Shusherina, N. P. *Russ. Chem. Rev.* **1974**, *43*, 851−861. (b) Afarinkia, K.; Vinader, V.; Nelson, T. D.; Posner, G. H. *Tetrahedron* **1992**, *48*, 9111−9171. (c) Woodward, B. T.; Posner, G. H. In *Advances in Cycloaddition*; Harmata, M., Ed.; JAI Press, Inc.: Greenwich, 1999; Vol. 5, pp 47−83.

(3) (a) Märkl, G.; Fuchs, R. *Tetrahedron Lett.* **1972**, 4691−4694. (b) Kraus, G. A.; Pezzanite, J. O. *J. Org. Chem.* **1982**, *47*, 4337−4340. (c) Moody, C. J.; Shah, P. *J. Chem. Soc., Perkin Trans 1* **1988**, 1407−1415. (d) Jackson, P. M.; Moody, C. J. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2156−2158. (e) Jackson, P. M.; Moody, C. J. *Tetrahedron* **1992**, *48*, 7447−7466. (f) Pérez, D.; Guitián, E.; Castedo, L. *J. Org. Chem.* **1992**, *57*, 5911−5917. (g) Cimetière, B.; Dubuffet, T.; Muller, O.; Descombes, J.-J.; Simonet, S.; Laubie, M.; Verbeuren, T. J.; Lavielle, G. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1375−1380. (h) Zhang, Y.; Herndon, J. W. *Tetrahedron Lett.* **2001**, *42*, 777−779.

10.1021/ol034852q CCC: $25.00

similar to those obtained with normal alkynes.[3a,d,e,4] With other alkenes, in some cases stable carbon dioxide-containing adducts are obtained,[2,5] whereas in others, carbon dioxide is spontaneously eliminated, providing a new diene system, which can cycloadd the second molecule of a dienophile to form a double cycloadduct.[2,6] In some cases, in the presence of an oxidant (quinone derivative, Ag_2O, $Pb(OAc)_4$, Pd/C or an enzyme), the intermediary diene was transformed to the aromatized system.[4b,6b,7] We believe that such a reaction, in the absence of an oxidant, was described by Saito et al., where the corresponding benzoazepine derivative was isolated in a 5% yield.[7b] Another example is the transformation of 6-indolizinyl-4-methyl-2*H*-pyran-2-one with *p*-benzoquinone into an aromatized derivative, where at least a part of the product does not appear as a result of oxidation by benzoquinone.[6b] In the conversion of pyrano[3,4-*b*]indol-3-ones with some alkenes, aromatized carbazole derivatives were formed by a cycloaddition followed by a 1,5-H shift.[4b,7f] There are a number of literature reports on benz[*e*]isoindoles;[8] some of them were described as potential agents for the symptomatic treatment of benign prostatic hyperplasia.[8d]

We envisaged the possibility of using a reaction between different fused pyran-2-ones **1** and appropriate maleimides **2** (via intermediates **3** and **4**), either for the formation of a new class[6d,9] of fused, highly substituted double cycloadducts **6** or, if the reaction could be stopped after the first cycloaddition step of maleimide and the elimination of hydrogen could be triggered, for the preparation of substituted benz[*e*]isoindoles **5**.

Starting from **1a−d** and the N-substituted maleimides **2a−c** in boiling decalin, we isolated the corresponding benz[*e*]isoindoles **5a−k** (Scheme 1, Tables 1 and 2). Since the reaction times were relatively long, we tried using some Lewis acids ($ZrCl_4$, $Yb(OTf)_3$) as catalysts to accelerate the reaction, but without any success. To get an insight into the reaction mechanism, we decided to stop some reactions after 1.5 h of reflux, and obtained the corresponding bicyclo[2.2.2]-octene derivatives **6a−c** as the major products (together with lesser amounts of benz[*e*]isoindoles **5** and unreacted starting pyran-2-ones **1**) (Table 2, runs 12−14).[12]

Scheme 1

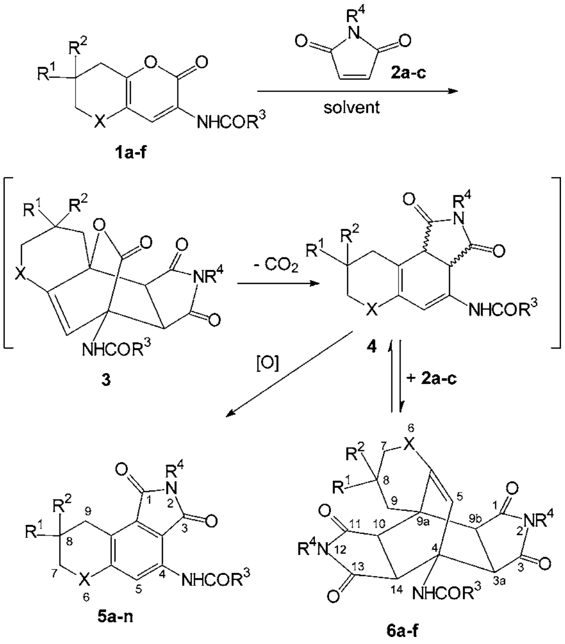


Table 1. Starting Compounds **1a−f** and **2a−c**

fused pyran-2-ones **1**					maleimides **2**	
	R^1	R^2	R^3	X		R^4
1a[10]	Me	Me	Ph	C═O	**2a**	Ph
1b[10]	Me	H	Ph	C═O	**2b**	Et
1c[10]	H	H	Ph	C═O	**2c**	Me
1d[11]	H	H	4-pyridyl	C═O		
1e[6d]	H	H	Ph	$-CH_2-$		
1f[6d]	H	H	Ph	$-[CH_2]_2-$		

From a comparison of runs 2, 5, and 8 with runs 12−14 it is evident that at least some of the benz[*e*]isoindole

---

[4] (a) Van Broeck, P. I.; Vanderzande, D. J.; Kiekens, E. G.; Hoornaert, G. J. *J. Chem. Soc., Perkin Trans. 1* **1991**, 639−644. (b) Van Broeck, P. I.; Van Doren, P. E.; Toppet, S. M.; Hoornaert, G. J. *J. Chem. Soc., Perkin Trans. 1* **1992**, 415−419. (c) Boger, D. L.; Takahashi, K. *J. Am. Chem. Soc.* **1995**, *117*, 12452−12459. (d) Balázs, L.; Kádas, I.; Töke, L. *Tetrahedron Lett.* **2000**, *41*, 7583−7587.

[5] See, for example: Markó, I. E.; Warriner S. L.; Augustyns, B. *Org. Lett.* **2000**, *2*, 3123−3125.

[6] See, for example: (a) Diels, O.; Alder, K. *Justus Liebigs Ann. Chem.* **1931**, *490*, 257−266. (b) Shimo, T.; Ohe, M.; Somekawa, K.; Tsuge, O. *J. Heterocycl. Chem.* **1991**, *28*, 1831−1833. (c) Nicolaides, D. N.; Bezergiannidou-Balouctsi, C.; Wajih Awad, R.; Litinas, K. E.; Malamidou-Xenikaki, E. *J. Org. Chem.* **1997**, *62*, 499−502. (d) Kranjc, K.; Leban, I.; Polanc, S.; Kočevar, M. *Heterocycles* **2002**, *58*, 183−190.

[7] (a) Cano, P.; Echavarren, A.; Prados, P.; Fariña, F. *J. Org. Chem.* **1983**, *48*, 5373−5376. (b) Saito, K.; Iida, S.; Mukai, T. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 3483−3487. (c) Jung, M. E.; Lowe, J. A., III; Lyster, M. A.; Node, M.; Pfluger, R. W.; Brown, R. W. *Tetrahedron* **1984**, *40*, 4751−4766. (d) Noguchi, M.; Kakimoto, S.; Kawakami, H.; Kajigaeshi, S. *Heterocycles* **1985**, *23*, 1085−1088. (e) Ahmed, S. A.; Bardshiri, E.; Simpson, T. J. *J. Chem. Soc., Chem. Commun.* **1987**, 883−884. (f) Van Doren, P.; Vanderzande, D.; Toppet, S.; Hoornaert, G. *Tetrahedron* **1989**, *45*, 6761−6770. (g) Karmarkar, K. S.; Samant, S. D. *Indian J. Chem. Sect. B* **1993**, *32*, 1113−1118. (h) Matsushita, Y−i.; Sakamoto, K.; Murakami, T.; Matsui, T. *Synth. Commun.* **1994**, *24*, 3307−3313. (i) Ose, T.; Watanabe, K.; Mie, T.; Honma, M.; Watanabe, H.; Yao, M.; Oikawa, H.; Tanaka, I. *Nature* **2003**, *422*, 185−189.

[8] (a) Bornstein, J.; McGowan, D. A.; DiSalvo, A. L.; Shields, J. E.; Kopecký, J. *J. Chem Soc., Chem. Commun.* **1971**, 1503−1504. (b) Andrews, M. D.; Brewster, A. G.; Chuhan, J.; Ibbett, A. J.; Moloney, M. G.; Prout, K.; Watkin, D. *Synthesis* **1997**, 305−308. (c) Ahmed, A.; Clayden, J.; Rowley, M. *Chem. Commun.* **1998**, 297−298. (d) Meyer, M. D.; Altenbach, R. J.; Basha, F. Z.; Carroll, W. A.; Condon, S.; Elmore, S. W.; Kerwin, J. F., Jr.; Sippy, K. B.; Tietje, K.; Wendt, M. D.; Hancock, A. A.; Brune, M. E.; Buckner, S. A.; Drizin, I. *J. Med. Chem.* **2000**, *43*, 1586−1603. (e) Berger, D.; Imhof, W. *Tetrahedron* **2000**, *56*, 2015−2023.

[9] Kende, A. S.; Lan, J.; Arad, D. *Tetrahedron Lett.* **2002**, *43*, 5237−5239.

[10] Kepe, V.; Kočevar, M.; Polanc, S.; Verček, B.; Tišler, M. *Tetrahedron* **1990**, *46*, 2081−2088.

[11] Černigoj-Marzi, A.; Polanc, S.; Kočevar, M. *J. Heterocycl. Chem.* **1997**, *34*, 1753−1756.

[12] **General Procedure.** A mixture of 2*H*-1-benzopyran-2-one (**1a−f**) (1 mmol) and N-substituted maleimide (**2a−c**) (2.2 mmol) was refluxed in 3 mL of solvent (Table 2). Thereafter, the solvent was evaporated under reduced pressure, the residue was treated with MeOH (2−3 mL), and the precipitated solid was filtered off and washed with MeOH (0.5−1 mL). The crude products thus obtained were crystallized for the analyses. When

Table 2. Reaction Conditions and Yields of Uncatalyzed Reactions

run	starting **1** and **2**		*t* (h)	yield (%)	product(s)
1	**1a**	**2a**	20[a]	86[b]	**5a**
2	**1a**	**2b**	21.5[a]	90[b]	**5b**
3	**1a**	**2c**	22.25[a]	76[b]	**5c**
4	**1b**	**2a**	22[a]	69[b]	**5d**
5	**1b**	**2b**	24[a]	60[b]	**5e**
6	**1b**	**2c**	22[a]	54[b]	**5f**
7	**1c**	**2a**	22[a]	65[b]	**5g**
8	**1c**	**2b**	27.5[a]	66[b]	**5h**
9	**1c**	**2c**	21.5[a]	63[b]	**5i**
10	**1d**	**2b**	25[a]	62[b]	**5j**
11	**1d**	**2c**	26.75[a]	56[b]	**5k**
12	**1a**	**2b**	1.5[a]	**1a** + **5b** + **6a** (0.1:0.3:1)[c,d]	
13	**1b**	**2b**	1.5[a]	**1b** + **5e** + **6b** (0.4:1:1)[c,d]	
14	**1c**	**2b**	1.5[a]	**1c** + **5h** + **6c** (0.2:0.3:1)[c,d]	
15	**1e**	**2b**	8.75[e]	56[b]	**6d**

[a] Decalin. [b] Yield of isolated compound. [c] After evaporation of solvent. [d] Estimated from ^{1}H NMR spectra. [e] Toluene.

products **5b**,**e**,**h** in runs 2, 5, and 8 must have resulted from the initially formed bicyclo[2.2.2]octene double cycloadducts **6a**−**c**, most probably via a retro Diels−Alder reaction. To prove this conjecture, we refluxed pure bicyclo[2.2.2]octene adduct **6a** in decalin, and after 24 h, we obtained a mixture of the corresponding benz[*e*]isoindole compound **5b** and the unreacted starting **6a** (ratio 0.1:1, as determined from the ^{1}H NMR spectrum of the crude mixture), whereas the same reaction carried out in the presence of the corresponding 5,6,7,8-tetrahydro-2*H*-1-benzopyran-2-one **1a** (in the molar ratio **6a**/**1a** = 1:1), gave exclusively the corresponding benz[*e*]isoindole **5b** (yield 98%), after 24 h of reflux, thus proving our assumption. It is interesting to note that under an inert atmosphere (argon) the oxidation from **4** to **5** proceeds as well, suggesting that this step is a disproportionation reaction involving the loss of hydrogen gas or an elimination of hydrogen with the assistance of a compound in the reaction mixture.[13] As a result of this, we decided to perform our reaction in the presence of a heterogeneous dehydrogenation catalyst,[14] and so we shortened the reaction times for the previous two examples (synthesis of **5b**) from 24 to 6 h, when 20 mol % of 5% Rh/C was added to the reaction mixture. On the basis of our findings, we are able to propose the reaction pathway shown in Scheme 1 (with the reaction step **4** to **6** being reversible). Despite the result of Saito,[7d] our reaction is the first really efficient transformation of a pyran-2-one ring with an alkene into an aromatized benzene ring. Encouraged by these results, we performed a synthesis of the compounds **5a**−**h** in the presence of Rh/C and significantly shortened the reaction times (Table 3). Isolated yields were nearly the same as in the absence of a catalyst, though the isolation procedure was more complex.[12]

Table 3. Reaction Conditions and Yields of Reactions Promoted with Rh/C (and Pd/C) in Decalin

run	starting **1** and **2**		*t* (h)	yield (%)	product(s)
1	**1a**	**2a**	3[a]	76[b]	**5a**
2	**1a**	**2b**	3.5[a]	85[b]	**5b**
3	**1a**	**2c**	8[a]	71[b]	**5c**
4	**1b**	**2a**	3[a]	65[b]	**5d**
5	**1b**	**2b**	3.5[a]	58[b]	**5e**
6	**1b**	**2c**	6[a]	50[b]	**5f**
7	**1c**	**2a**	3.5[a]	63[b]	**5g**
8	**1c**	**2b**	3[a]	59[b]	**5h**
9	**1e**	**2b**	10[a]	64[d]	**5l** + **7** (1:1)[e]
10	**1e**	**2b**	92[c]	69[b]	**7**
11	**1f**	**2a**	10[a]	58[d]	**5m** + **6e** (1:0.6)[e]
12	**1f**	**2b**	24[f]	61[d]	**5n** + **6f** (1:0.8)[e]
13	**1f**	**2b**	24[a]	65[d]	**5n** + **6f** (1:0.4)[e]

[a] With 20 mol % of Rh/C (5%). [b] Yield of isolated product. [c] 78 mol % of Rh/C (5%). [d] Yield of crude product. [e] Estimated from ^{1}H NMR spectra. [f] 20 mol % of Pd/C (10%).

Having in mind the unprecedented nature of our transformation, we wanted to extend it to other pyran-2-one-ring-containing systems. In the reaction between the 5-unsubstituted benzopyran-2-one derivative **1e**[6d] and the maleimide **2b** in boiling toluene the bicyclo[2.2.2]octene derivative **6d** was isolated as a single product (Table 2, run 15), while the use of decalin caused the formation of some aromatized byproduct (of type **5**). To produce a larger amount of the benz[*e*]isoindole derivative we tried longer heating times (up to 30 h), increasing the molar ratio of diene/dienophile, bubbling oxygen through the reaction mixture, and possible oxidants, like those used by other groups[7] (Ag_2O, MnO_2), but these did not cause the oxidation to proceed to an appreciable extent (as evident from the TLC monitoring of the reaction progress and from the ^{1}H NMR spectra of the unpurified products). This result prompted us to try again with some dehydrogenation catalysts, and indeed Rh/C and Pd/C enabled us to synthesize the benz[*e*]isoindole derivatives. When using 20 mol % of Rh/C (5%) in the reaction of **1e** and **2b** (run 9, Table 3), after 10 h, besides the expected 6,7,8,9-tetrahydro derivative **5l**, the completely aromatized benz[*e*]isoindole derivative **7** (Figure 1) was formed as well (approximate ratio 1:1, based on the ^{1}H NMR spectrum), together with a small amount of the corresponding double cycloadduct (**6d**, less than 10% yield). When we increased the reaction time (to 35 h) and the amount of Rh/C used (to 82 mol %), the major product obtained was fused naphthalene derivative **7**, with a minor amount of **5l** (the approximate ratio from the ^{1}H NMR spectrum was 1:0.18), whereas no double cycloadduct **6d** was formed at all. With an even

---

5% Rh/C was added to the reaction mixture (10 mL of decalin), the reaction mixture was filtered after heating, the remaining solid was extracted 3−5 times with boiling toluene, and the extracts (including decalin) were combined and evaporated under reduced pressure to obtain the crude products.

(13) Some crude reaction mixtures were investigated by ^{1}H NMR spectroscopy and show the presence of signals that could be ascribed to N-substituted succinimides, thus supporting the idea that maleimides serve as acceptors of hydrogen. In the case of run 2 we also confirmed this assumption by adding an authentic *N*-ethylsuccinimide to the crude mixture of products.

(14) (a) Fu, P. P.; Harvey, R. G. *Chem. Rev.* **1978**, *78*, 317−361. (b) Hudlický, M. *Oxidations in Organic Chemistry*; ACS Monograph 186; American Chemical Society: Washington, DC, 1990.

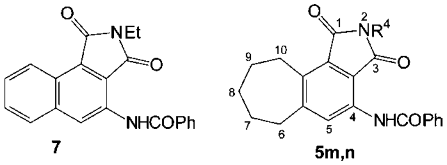


Figure 1.

longer reaction time (run 10, Table 3; 78 mol % of Rh/C), only product **7** was obtained. On the basis of these findings, we continued with our studies of related fused pyran-2-one **1f**[6d] (where there is no possibility of producing a fused benzene ring). This compound shows the same reactivity pattern, producing bicyclo[2.2.2]octene derivatives in the absence of a dehydrogenation catalyst, regardless of the imide **2** used. But when employing Rh/C, products of type **5** are formed (Table 3, runs 11−13); however, a substantial amount of adducts of type **6** are produced as well. With the increase in the amount of Rh/C used and with increasing reaction times, there is a tendency to produce higher ratios of **5**:**6**. On the other hand, a decrease in the amount of maleimide **2** used, only lengthens the reaction times and leaves a part of the initial fused pyran-2-one **1** unreacted as well. From the reaction of **1f** with **2b** (Table 3, runs 12 and 13) it is evident, that it is better to use Rh/C than Pd/C.

The structures of the benz[*e*]isoindole products **5a**−**k** were determined using standard spectroscopic techniques. It is evident that the signals with the chemical shifts within the range 9.47−9.63 ppm belong to the 5-H. In the case of double cycloadducts **6a**−**f**, the NMR spectra indicate the presence of a plane of symmetry (eliminating the possible *endo,exo*-type of adducts).[6d] On the basis of NOESY spectra (**6a** and **6e**) it is possible to ascribe the doublets (average coupling constant 8.1 Hz) with the chemical shifts inside the 2.93−3.26 ppm interval to the 9b-H, 10-H (10b-H, 11-H for **6e**,**f**) pair of protons, whereas the doublets inside the 4.17−4.51 ppm interval belong to the 3a-H, 14-H (3a-H, 15-H for **6e**,**f**) pair. The range of chemical shifts for these pairs of equivalent protons is very narrow (with $\Delta\delta$ being 0.33 and 0.34 ppm, respectively), suggesting that their environment is rather similar to the products of type **6**, indicating that they are all of the same structural type. The structures are consistent with the NOEs, which is similar to in our previous report, where we also determined the structures of the related adducts with maleic anhydride using an X-ray diffraction study.[6d]

To summarize, we presented an efficient synthesis of benz[*e*]isoindoles and related compounds of type **5** and a new type of bicyclo[2.2.2]octene derivatives **6**. Depending on the nature of the X fragment, we have been able to direct the reaction toward benz[*e*]isoindoles (when X is C═O) in a new substituent-driven transformation or to bicyclo[2.2.2]octenes (when X is a $[CH_2]_n$ fragment) with moderate to high yields.

It seems plausible that the 5-oxo group decreases the reactivity of the intermediate **4** for the cycloaddition of a second molecule of a dienophile **2** and thus enables the loss of hydrogen to take place. The products thus obtained (**5a**−**k**) seem to be the result of higher resonance stabilization, and also thermodynamically more favored than those not containing the 5-oxo moieties. It is worth mentioning that all these reactions proceed without using catalysts, though we have tried some. The use of Lewis acid catalysts neither shortened the reaction times, nor changed the yield or selectivity. The use of rhodium supported on activated charcoal as a dehydrogenation agent accelerates the reaction toward aromatized derivatives **5** (and **7**). A further investigation of the synthetic applicability of all the transformations mentioned here is under way.

Acknowledgment. We thank the Ministry of Education, Science and Sport of the Republic of Slovenia for financial support (P0-503-103). Dr. B. Kralj and Dr. D. Žigon (Centre for Mass Spectroscopy, “Jožef Stefan” Institute, Ljubljana, Slovenia) are gratefully acknowledged for the MS measurements.

Supporting Information Available: Characterization data for compounds **5a**−**k**,**m**,**n**, **6a**−**f**, and **7**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL034852Q