JOC Note

A Multicomponent Synthesis of Triazinane Diones

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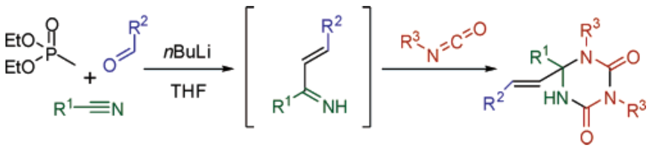
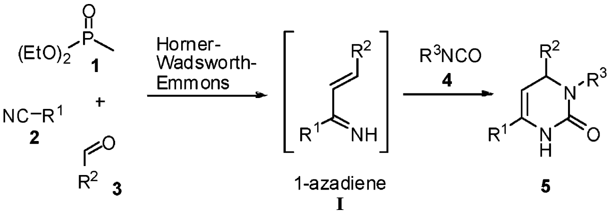


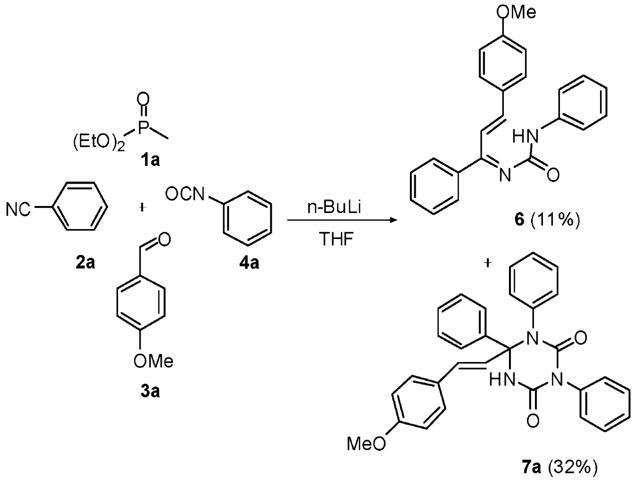
An efficient, one-pot synthetic protocol toward triazinane diones, a rather unexplored class of heterocyclic scaffolds combining phosphonates, nitriles, aldehydes, and isocyanates is described. The optimization of the reaction, synthesis of a small library of different triazinane diones, as well as alternative routes toward the triazinane dione scaffold are discussed.

Chemical space, defined as the total descriptor space including all carbon-based molecules that in principle can be prepared, contains more than 10^{60} small organic molecules.[1] Only a very limited number of these have been actually made by man and explored for potential useful properties, like their biological relevance. This continues to drive synthetic chemists to develop novel reactions that can efficiently access unexplored regions of chemical space. Especially appreciated are those methods that allow the quick generation of scaffold diversity.[2] Multicomponent reactions (MCRs) represent one of the most powerful tools to easily access molecules showing both skeletal and decoration diversity.[3] As such, these reactions are also ideally suited to uncover thus far unprecedented types of scaffolds. Recently, we described a novel four-component reaction (4-CR) that combines phosphonates **1**, aldehydes **2**, nitriles **3**, and isocyanates **4** to afford functionalized 3,4-dihydropyrimidine-2-ones (DHPMs, **5**) efficiently (Scheme 1).[4] The MCR most likely proceeds via 1-azadienes of type **I** that can undergo facile aza-Diels−Alder (aza-DA) cycloaddition with isocyanates **4**, equipped with an electron-withdrawing substituent, to give DHPMs of type **5**.

SCHEME 1. Synthesis of Dihydropyrimidine-2-ones



SCHEME 2. Formation of Noncyclized 6 and Triazinane Dione 7a



The thermodynamic driving force for a (concerted) aza-DA reaction of such 1-azadienes is, compared to butadienes or 2-azadienes, much lower.[5] Consequently, this results in a much lower reactivity toward dienophiles. Therefore, Diels−Alder reactions with 1-azadienes usually proceed sluggishly and are of limited synthetic significance.[6] During our initial studies, we observed the formation of noncyclized **6** together with triazinane dione **7a** when diethyl methylphosphonate **1a**, benzonitrile **2a**, 4-methoxybenzaldehyde **3a**, and PhNCO **4a** were combined (Scheme 2).[4a] The corresponding DHPM **5a** was not formed in this case. 6,6-Dialkyl/aryl-substituted triazinane diones such as **7** are a hitherto unexplored class of heterocyclic scaffolds and only scattered reports exist on their synthesis.[7] This led us to examine the reaction pathway more closely in order to optimize the MCR toward these highly interesting and novel cyclic urea derivatives.

Most likely, triazinane dione **7a** is formed via the pathway depicted in Scheme 3. Deprotonation of the phosponate **1a** with *n*-BuLi and subsequent reaction with **2a** yields the corresponding intermediate ketimine. A subsequent Horner−Wadsworth−Emmons reaction of this ketimine and **3a** results in the formation of the azadiene **Ia**. The isolation of the linear urea derivative **6** strongly supports a stepwise reaction mechanism, in which **6**

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(1) Dobson, M. *Nature* **2004**, *32*, 824.

(2) Burke, M. D.; Schreiber, S. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 46.

(3) (a) Dömling, A. *Chem. Rev.* **2006**, *106*, 17. (b) Zhu, J. *Eur. J. Org. Chem.* **2003**, 1133. (c) Orru, R. V. A.; De Greef, M. *Synthesis* **2003**, 1471.

(4) (a) Vugts, D. J.; Jansen, H.; Schmitz, R. F.; de Kanter, F. J. J.; Orru, R. V. A. *Chem. Commun.* **2003**, 2594. (b) Vugts, D. J.; Koningstein, M. M.; Schmitz, R. F.; de Kanter, F. J. J.; Groen, M. B.; Orru, R. V. A. *Chem. Eur. J.* **2006**, *12*, 7178.

(5) Jung, M. E.; Shapiro, J. J. *J. Am. Chem. Soc.* **1980**, *102*, 7862.

(6) Behforouz, M.; Ahmadian, M. *Tetrahedron* **2000**, *56*, 5259.

(7) (a) Etienne, A.; Bonte, B. *Bull. Soc. Chim. Fr.* **1975**, *5*−*6*, 1419. (b) Etienne, A.; Lonchambon, G.; Giraudeau, P. *Comptes Rendues* **1977**, *285*, 321. (c) Vovk, M. V.; Dorokhov, V. I.; Zhitomir, S.-kh. *Izv. Vyssh. Ucheb. Zaved. Khim. Khim. Tekhnol.* **1992**, *35*, 28. (d) Vovk, M. V. *Russ. J. Org. Chem.* **1996**, *32*, 767. (e) Nazarenko, K. G.; Shvidenko, K. V.; Pinchuk, A. M.; Tolmachew, A. A. *Monatsh. Chem.* **2005**, *136*, 211.

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SCHEME 3. Mechanism for the Formation of Triazinane Diones

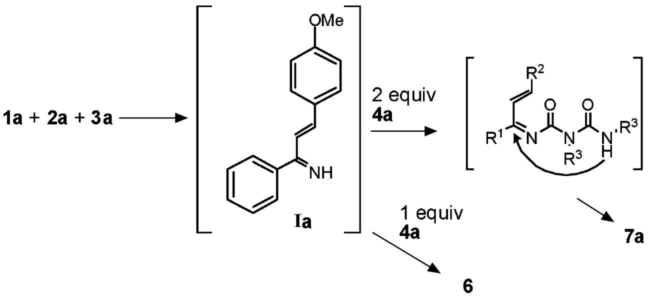


TABLE 1. Optimization of the Formation of 7b

entry	equiv of **4a**	reaction time	yield (%)	workup[a]
1	1.1	18 h	20	A
2	1.1	5 min	29	A
3	2.2	5 min	80	A
4	2.2	5 min	91	B

[a] Key: (A) After addition of Et_2O, the reaction mixture was washed with water and brine. Drying the organic phase and evaporation of the solvents followed by column chromatography afforded pure **7b**. (B) After partial evaporation of the solvents, water was added to the reaction mixture. The product precipitated, and after filtering and washing with cold Et_2O, pure **7b** was obtained directly.

can be formed from an addition reaction of **Ia** to **4a** followed by a 1,3-H-shift. Moreover, formation of the triazinane dione can be rationalized by the addition of a second equivalent of **4a** followed by ring closure to afford the thermodynamically favored six-membered cyclic urea derivative.

The moderate isolated yield of **7a** encouraged us to further optimize the reaction and explore the scope of this interesting multicomponent procedure. For convenience, the combination of **1a**, **2a**, benzaldehyde **3b**, and **4a** was employed to optimize the reaction conditions toward the corresponding triazinane dione **7b**. As a starting point, the general conditions for the efficient formation of the DHPM derivative **5b** were chosen.[4b] Not surprisingly, the standard conditions afforded mostly **5b**, and the desired triazinane dione **7b** was observed in only 20% yield (Table 1, entry 1). However, when product formation was followed in time by HPLC analysis it became clear that the formation of **7b** was instantaneous. The conversion to **7b** was at its maximum only minutes after addition of **4a** and decreased slowly over time.

Thus, immediate workup after the addition of the final isocyanate component already showed a significant improvement of the yield of **7b** (entry 2, 29%). The MCR was further optimized by slight modification of the workup procedure and using 2.2 equiv of isocyanate **4a**. Addition of water during workup caused precipitation of the product from the reaction mixture, and **7b** could simply be filtered off and washed with diethyl ether to yield the pure product in 91% isolated yield (entry 4).

With this optimized procedure in hand, the scope of the reaction toward a range of differently substituted triazinane diones was studied. As becomes clear from Figure 1, the reaction is quite flexible and isolated yields of the corresponding triazinane diones **7** are usually reasonable to good (25−91%). Successful inputs include nitriles (**2**) and aldehydes (**3**) with (hetero)aromatic and aliphatic substituents R^1 and R^2. For the isocyanate input (**4**) benzylic and aromatic substituents R^3 are compatible in this reaction. The reaction employing an isocyanate with an aliphatic R^3 group is less efficient (**7l**, 13%).

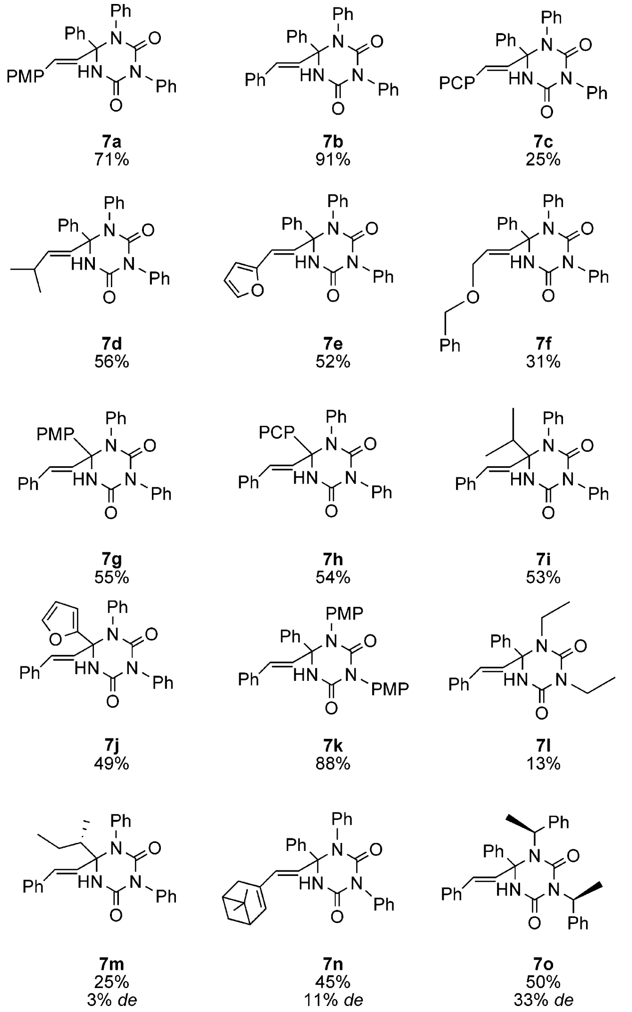
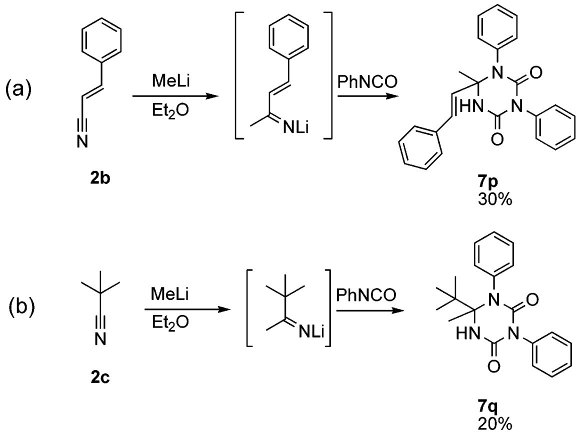


FIGURE 1. Range of differently substituted triazinane diones. PMP = *p*-methoxyphenyl, PCP = *p*-chlorophenyl.

Although the MCR proceeds smoothly using either an optically pure nitrile, aldehyde, or isocyanate, the observed diastereoselectivities are not very encouraging (**7m**−**o**). With (*S*)-2-methylbutyronitrile, low stereoinduction is perhaps not surprising considering the rather basic reaction conditions. On the other hand, for the DHPM synthesis the use of the optically pure (*R*)-myrtenal was relatively successful, and a de up to 85% was observed.[4b] However, application of (*R*)-myrtenal did not result in a diastereoselective formation of the corresponding triazinane dione **7n**. The best (albeit still moderate) diastereoselectivity was observed when (*S*)-α-methyl benzyl isocyanate was combined with **1a**, **2a**, and **3a** under the standardized conditions for the formation of **7o** (de = 33%).

As for the DHPM synthesis, the most limiting input in the MCR for triazinane diones is, however, the phosphonate input. From our earlier studies, it is known that only the use of diethyl methylphosphonate or diethyl ethylphosphonate resulted in efficient formation of the crucial 1-azadiene intermediate **I**.[4b] Partly based on some literature precedents,[8] some alternative methods were investigated for the in situ generation of 1-azadienes **I** and their subsequent trapping by PhNCO **4a**. Attempts

SCHEME 4. Alternative Route toward Triazinane Diones



starting from α,*β*-unsaturated aldehydes, like the addition of appropriate Grignard reagents to nitriles or reduction of α,*β*-unsaturated nitriles with DIBAL-H, were not successful and gave mixtures of unidentified products. The only procedure that indeed led to the formation of a triazinane dione is depicted in Scheme 4a.

Thus, the reaction of α,*β*-unsaturated nitrile **2b** with MeLi and subsequent reaction with PhNCO **4a** gave the corresponding triazinane dione **7p**, albeit in only 30% isolated yield.

Alternatively, efficient triazinane dione formation may occur by trapping an intermediate imine, instead of a 1-azadiene, with an appropriate isocyanate. Indeed, when MeLi was added to nitrile **2c** followed by the addition of PhNCO **4a** the desired product **7q** was obtained, but again only in a disappointing 20% yield (Scheme 4b). Since our MCR efficiently affords quite a range of differently functionalized triazinane diones we did not pursue further in this direction.

In conclusion, we have developed a flexible multicomponent synthesis of a range of differently functionalized triazinane diones. Our approach opens the way to more detailed studies of the general and biological properties of these cyclic urea-type scaffolds, which have hitherto remained unexplored. The application of this scaffold in the synthesis of some unnatural nucleoside analogues is currently under investigation in our laboratories and will be reported in due course.

Experimental Section

General Procedure for the Synthesis of Triazinanediones. To a solution of diethyl methylphosphonate (152 mg, 1.0 mmol) in dry THF (5 mL) at −78 °C was added *n*-BuLi (1.2 mmol, 1.6 M in hexanes), and this mixture was stirred for 1.5 h at this temperature. The nitrile was added, and stirring was continued at −78 °C for 45 min. Then the reaction mixture was warmed to −40 °C, stirred for 1 h, and subsequently warmed to −5 °C and stirred for 30 min. The aldehyde was then added, and the reaction mixture was stirred at −5 °C for 30 min, warmed to room temperature, and stirred for an additional 1.5 h. The isocyanate was then added, and after 5 min, the reaction was worked up by removing half of the solvent by evaporation under reduced pressure and addition of water (10 mL). In some cases, triazinane diones **7** either crystallized directly from this mixture or crystallized upon standing overnight at 5 °C. Pure products were obtained by filtration and washing of the residue with cold Et_2O. In cases where triazinane diones **7** did not crystallize from the reaction mixture, the products were purified by flash chromatography or by recrystallization from hexane/EtOAc. For compounds **7e**,**g**−**k**, the products were co-evaporated with Et_2O and dried 48 h under vacuum (10^{-2} mbar) to remove traces of solvents.

Triazinanedione 7a. Following the general procedure, reaction between diethyl methylphosphonate (152 mg, 1.0 mmol), benzonitrile (113 mg, 1.1 mmol), *p*-methoxybenzaldehyde (150 mg, 1.1 mmol), and phenyl isocyanate (262 mg, 2.2 mmol) followed by crystallization from hexane/EtOAc afforded **7a** (340 mg, 71%) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.59−7.57 (m, 2H), 7.39−7.33 (m, 7H), 7.30 (d, $J = 8.7$ Hz, 1H), 7.20−7.11 (m, 7H), 6.91 (d, $J = 15.7$ Hz, 1H), 6.89 (d, $J = 8.7$ Hz, 1H), 6.39 (d, $J = 15.9$ Hz, 2H). 6.16 (s, 1H), 3.83 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 160.3, 152.9, 152.5, 139.9, 137.7, 135.0, 132.4, 129.7 (2C), 129.5, 129.2 (2C), 128.9 (2C), 128.7 (2C), 128.6 (2C), 128.37 (2C), 128.35, 127.7, 127.6 (2C), 127.5, 125.6, 114.3 (2C), 75.8, 55.4; HRMS (FAB) calcd for $C_{30}H_{25}N_3O_3$ (MH^+) 476.1974, found 476.1970; IR (KBr) 3435 (m), 3207 (w), 3090 (w), 1720 (s), 1680 (s), 1513 (m), 1435 (s), 1321 (m), 1256 (m), 741 (m), 694 (m), 592 (m), 536 (m); mp 177.4−178.4 °C.

Triazinanedione 7b. Following the general procedure, reaction between diethyl methylphosphonate (152 mg, 1.0 mmol), benzonitrile (113 mg, 1.1 mmol), benzaldehyde (117 mg, 1.1 mmol), and phenyl isocyanate (262 mg, 2.2 mmol) afforded crude **7b**. The crude product precipitated out of the reaction mixture after evaporation of half of the solvent and addition of water (10 mL). Subsequent washing of the crude product with cold Et_2O gave **7b** (406 mg, 91%) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 9.32 (s, 1H), 7.62−7.60 (m, 2H), 7.47−7.30 (m, 11H), 7.24−7.12 (m, 5H), 7.06−7.04 (m, 2H), 6.78 (d, $J = 16.0$ Hz, 1H), 6.62 (d, $J = 16.0$ Hz, 1H); ^{13}C NMR (101 MHz, DMSO-d_6) δ (ppm) 153.5, 152.9, 141.3, 138.9, 136.6, 136.1, 132.8, 130.7 (2C), 130.3 (2C), 129.8, 129.7 (2C), 129.7, 129.4, 129.4 (2C), 129.3 (2C), 129.2 (2C), 128.6, 128.6 (2C), 128.1, 127.8 (2C), 76.2; HRMS (FAB) calcd for $C_{29}H_{23}N_3O_2$ (MH^+) 446.1869, found 446.1872; IR (KBr) 3436 (m), 3208 (w), 3085 (w), 1721 (s), 1682 (s), 1493 (m), 1443 (s), 1330 (m), 752 (m), 694 (m), 596 (m), 535 (m); mp 169.0 −170.9 °C dec.

Triazinanedione 7p. Dry Et_2O (2 mL) was cooled to −78 °C, and MeLi (625 μL, 1.6 M in Et_2O) was added. Cinnamonitrile (129 mg, 1.0 mmol) dissolved in dry Et_2O (2 mL) was added dropwise to this solution over a period of 30 min, and the mixture was then stirred at −78 °C for 3 h and at room temperature for 1 h. Phenyl isocyanate (217 μL, 2.0 mmol) was added, and after 5 min, the reaction was worked up by addition of H_2O (10 mL). Solid materials were filtered off, washed with cold Et_2O, dissolved in DCM, and evaporated. Both the solid material and the Et_2O wash contained product, so they were purified together by column chromatography (hexane/EtOAc 2:1) to afford **7p** (115 mg, 30%) as a yellow solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41−7.25 (m, 15H), 6.80 (d, $J = 15.9$ Hz, 1H)., 6.41 (d, $J = 15.9$ Hz, 1H), 5.94 (s), 1.59 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.1, 152.4, 136.9, 135.2, 135.0, 130.1 (2C), 129.5, 129.3 (2C), 129.2 (2C), 128.9 (2C), 128.8 (2C), 128.7, 128.6, 128.3, 126.9 (2C), 70.6, 26.7; HRMS (EI, 70 eV) calcd for $C_{24}H_{21}N_3O_2$ (M^+) 383.1634, found 383.1632; IR (KBr) 3270 (w), 2925 (w), 1716 (s), 1674 (s), 1461(m), 1329 (m), 968 (w), 760 (m), 698 (m); mp 223.0−223.6 °C dec.

Triazinanedione 7q. Dry Et_2O (2 mL) was cooled to −78 °C, and MeLi (625 μL, 1.6 M in Et_2O) was added. Trimethylacetonitrile (83 mg, 1.0 mmol) dissolved in dry Et_2O (2 mL) was added dropwise to this solution over a period of 30 min, and the mixture was then stirred at −78 °C for 3 h and at room temperature for 1 h. Phenyl isocyanate (217 μL, 2.0 mmol) was added, and after 5

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(8) (a) Toye, T.; Ghosez, L. *J. Am. Chem. Soc.* **1975**, *97*, 2276. (b) Blechert, S.; Wirth, T. *Tetrahedron Lett.* **1991**, *32*, 7237. (c) Langhals, H.; Ruchardt, C. *Chem. Ber.* **1981**, *114*, 3831. (d) Babler, J. H.; Marcuccilli, C. J. *Tetrahedron Lett.* **1987**, *28*, 4657. (e) Klein Gebbink, E. A.; Stork, G. A.; Jansen, B. J. M.; de Groot, A. *Tetrahedron* **1999**, *55*, 11077. (f) Sulmon, P.; De Kimpe, N.; Schamp, N. *J. Chem. Soc., Chem. Commun.* **1985**, *11*, 715.

min, the reaction was worked up by addition of H_2O (10 mL). Solid materials were filtered off, washed with cold Et_2O, dissolved in DCM, and evaporated. Both the solid material and the Et_2O wash contained product so they were purified together by column chromatography (hexane/EtOAc 4:1) to afford **7q** (67 mg, 20%) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39−7.25 (m, 10H), 6.07 (s, 1H), 1.52 (s, 3H), 1.20 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.1, 152.0, 138.8, 135.1, 132.7, 130.9, 128.8 (2C), 128.7 (2C), 128.7, 128.5, 128.3, 125.1, 76.3, 44.1, 26.5 (3C), 24.8; HRMS (EI, 70 eV) calcd for $C_{20}H_{23}N_3O_2$ (M^+) 337.1790, found 337.1790; IR (KBr) 3206 (m), 3099 (m), 2978 (m), 1722 (s), 1677 (s), 1457 (s), 1325 (s), 769 (s), 700 (s), 589 (m), 562 (m); mp 219.2−220.2 °C dec.

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Supporting Information Available: Experimental procedures and characterization data for compounds **7c−o** and ^{1}H and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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