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An Intramolecular PIFA-Mediated Metal-Free Allylic Oxycarbonylation Reaction and Its Application to the Preparation of Furopyrimidinones

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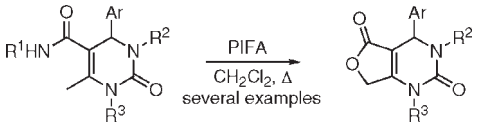
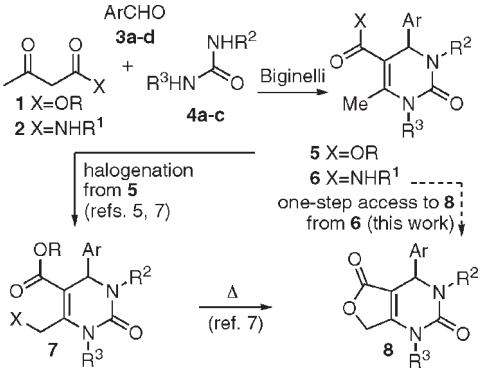
Received September 13, 2010



The preparation of a series of furo[3,4-*d*]pyrimidinones by an unprecedented PIFA-mediated intramolecular allylic oxycarbonylation reaction developed on 5-carbamoyl-substituted Biginelli adducts is presented. The construction of the fused lactone by a metal-free C−H activation process, without the need of an additional functionalization step, is featured in the present work.

Organic chemists have found in the development of known and new multicomponent reactions (MCRs) an inspiration to quickly design straightforward entrances to large families of novel compounds, especially when these syntheses are coupled with combinatorial strategies.[1] Among them, the venerable 3-MCR Biginelli reaction[2] has recently experienced a renovated impulse based, primarily, on the discovery of many different catalysts that allow the preparation of the resultant dihydropyrimidines (DHPMs) with excellent results, as opposed to the limited success encountered in the original reports,[3] but also, and more importantly, due to a number of different post-transformations that can be developed on such a privileged structure in the search for highly elaborated skeletons with potential pharmacological action. In this context, functionalization of the C-6 position, with the aim to construct a fused ring, has been the matter of recent research. In particular, furo[3,4-*d*]pyrimidinones of type **8** have been identified as selective α_{1a}-adrenergic receptor antagonists, and hence have potential use for the treatment of benign prostatic hyperplasia (BPH), as well as agents that show calcium channel blocking activity.[4] The highly limited number of routes available for the preparation of **8** are usually designed to prepare intermediate **7**, either by allylic halogenation of **5**[5] or directly from 4-halo-3-ketoesteres of type **1**,[6] and then to transform it into the final bicyclic compound by simple heating (Scheme 1).[7]

SCHEME 1



During the past few years we have been involved in a long-lasting project related to the application of the hypervalent iodine reagents[8] in the synthesis of nitrogen-containing heterocycles. In particular, we have taken advantage of the ability of PIFA [phenyliodine(III) bis(trifluoroacetate)] to generate *N*-acylnitrenium ions from aryl-, olefin-, or alkyne-substituted amides as an efficient strategy for the intramolecular construction of new C−N bonds.[9] Now, we present an extension

(1) (a) Ganem, B. *Acc. Chem. Res.* **2009**, *42*, 463–472. (b) Armstrong, R. W.; Combs, A. P.; Tempest, P. A.; Brown, S. D.; Keating, T. A. *Acc. Chem. Res.* **1996**, *29*, 123–131.

(2) For some selected reviews on the Biginelli reaction, see: (a) Kappe, C. O. *Org. React.* **2004**, *63*, 1–116. (b) Kappe, C. O. *Acc. Chem. Res.* **2000**, *33*, 879–888. (c) Kappe, C. O. *Tetrahedron* **1993**, *49*, 6937–6963.

(3) Biginelli, P. *Gazz. Chim. Ital.* **1893**, *23*, 360–416.

(4) For the pharmacological action of these systems see, for example: (a) Kirby, R. S.; Christmas, T. J. *Benign Prostatic Hyperplasia*; Gower Medical Publishing: London, UK, 1993; p 1. (b) Kenny, B.; Ballard, S.; Blagg, J.; Fox, D. *J. Med. Chem.* **1997**, *40*, 1293–1315. (c) Kappe, C. O. *Eur. J. Med. Chem.* **2000**, *35*, 1043−1052 and references cited therein.

(5) (a) Zigeuner, G.; Hamberger, H.; Blaschke, H.; Sterk., H. *Monatsh. Chem.* **1966**, *97*, 1408–1421. (b) Singh, K.; Singh, S. *Tetrahedron* **2008**, *64*, 11718–11723. (c) See also ref 2c.

(6) Pérez, R.; Beryozkina, T.; Zbruyev, O. I.; Haas, W.; Kappe, C. O. *J. Comb. Chem.* **2002**, *4*, 501–510.

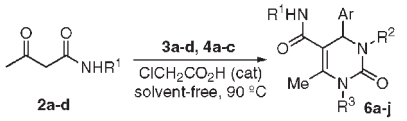
(7) See, for example: (a) Lagu, B.; Tian, D.; Chiu, G.; Nagarathnam, D.; Fang, J.; Shen, Q.; Forray, C.; Ransom, R. W.; Chang, R. S. L.; Vyas, K. P.; Zhang, K.; Gluchowski, C. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 175–178. (b) Takuo Chiba, T.; Sato, H.; Kato, T. *Heterocycles* **1984**, *22*, 493–496. (c) See also ref 6. (d) A similar multistep protocol to provide tricyclic furopyridines from halogenated Hantzsch adducts has been reported: Carroll, W. A.; Agrios, K. A.; Altenbach, R. J.; Buckner, S. A.; Chen, Y.; Coghlan, M. J.; Daza, A. V.; Drizin, I.; Gopalakrishnan, M.; Henry, R. F.; Kort, M. E.; Kym, P. R.; Milicic, I.; Smith, J. C.; Tang, R.; Turner, S. C.; Whiteaker, K. L.; Zhang, H.; Sullivan, J. P. *J. Med. Chem.* **2004**, *47*, 3180–3192.

(8) For some excellent books on the chemistry of hypervalent iodine reagents, see: (a) Varvoglis, A. *The Organic Chemistry of Polycoordinated Iodine*; VCH: New York, 1992. (b) Varvoglis, A. *Hypervalent Iodine in Organic Synthesis*; Academic Press: London, UK, 1997. (c) Wirth, T., Ed. *Hypervalent Iodine Chemistry*; Springer-Verlag: Berlin, Germany, 2003. For some recent reviews on the same topic, see: (d) Ciufolini, M. A.; Braun, N. A.; Canesi, S.; Ousmer, M.; Chang, J.; Chai, D. *Synthesis* **2007**, 3759–3772. (e) Canty, A. J.; Rodemann, T.; Ryan, J. H. *Adv. Organomet. Chem.* **2008**, *5*, 279–313. (f) Quideau, S.; Pouysegu, L.; Deffiieux, D. *Synlett* **2008**, 467–495. (g) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2008**, *108*, 5299–5358. (h) Zhdankin, V. V. *ARKIVOC* **2009**, *i*, 1–62. (i) Pouységu, L.; Deffieux, D.; Quideau, S. *Tetrahedron* **2010**, *66*, 2235–2261.

(9) For some selected contributions from our group, see: (a) Correa, A.; Tellitu, I.; Domínguez, E.; Moreno, I.; SanMartin, R. *J. Org. Chem.* **2005**, *70*, 2256–2264. (b) Tellitu, I.; Urrejola, A.; Serna, S.; Moreno, I.; Herrero, M. T.; Domínguez, E.; SanMartin, R.; Correa, A. *Eur. J. Org. Chem.* **2007**, 437–444. (c) Tellitu, I.; Serna, S.; Herrero, M. T.; Moreno, I.; Domínguez, E.; SanMartin, R. *J. Org. Chem.* **2007**, *72*, 1526–1529.

Published on Web 10/22/2010 DOI: 10.1021/jo101797s

SCHEME 2



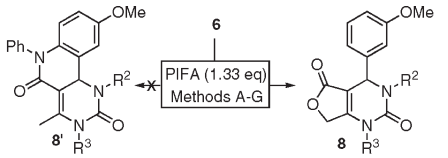
6 (%)	R^1	Ar	R^2	R^3
a (65)	C_6H_5	m-$MeOC_6H_4$	H	H
b (97)	C_6H_5	m-$MeOC_6H_4$	H	Me
c (36)	C_6H_5	m-$MeOC_6H_4$	Me	Me
d (43)	C_6H_5	C_6H_5	Me	Me
e (42)	p-$NO_2C_6H_4$	C_6H_5	Me	Me
f (21)	C_6H_5	m-$MeOC_6H_4$	Et	Et
g (51)	2,4-$Me_2C_6H_3$	C_6H_5	Me	Me
h (23)	H	C_6H_5	Me	Me
i (40)	C_6H_5	2-thienyl	Me	Me
j (42)	C_6H_5	o-$NO_2C_6H_4$	Me	Me

of this methodology to molecules containing an allylic position as an appealing metal-free route for the intramolecular oxycarbonylation of unfunctionalized H−C(sp^3) bonds.[10]

The preparation of the required substrates was conceived through the classical Biginelli multicomponent reaction. To shorten our synthetic proposal as much as possible, a series of 3-ketoamides of type **2** were selected to replace the ubiquitous 3-ketoesters that in almost all cases are employed, and to avoid, hence, additional hydrolysis/amidation steps. After evaluation of several catalysts and reaction conditions,[11] the use of chloroacetic acid (15% mol) under solvent-free conditions was selected to prepare a series of 5-carboxamido-DHPMs **6a**−**j** (see Scheme 2).[12]

Then, 5-carboxamido-DHPMs **6a**−**c** were initially selected to establish the optimal reaction conditions and the structural requirements for the PIFA-mediated cyclization step (see Scheme 3). These assays were conducted in the presence of a slight excess (1.33 equiv) of PIFA, using different solvents (CH_2Cl_2, trifluoroethanol, $CHCl_3$), at different temperatures (from rt to reflux), and with participation of different additives.[13] It was found that while the reaction carried out on 1,3-unsubstituted DHPM **6a** produced a complex mixture of compounds under any circumstance, 1-substituted DHPM **6b** rendered the desired heterocycle **8a**, although with limited success (18%). Finally, we found that starting from *N*,*N*′-disubstituted substrates (as in **6c**) was a critical structural prerequisite for the success of the reaction.[14] Therefore, from a variety of reaction conditions tested, the use of refluxing CH_2Cl_2 as solvent (Method B) was selected as the best option to prepare the corresponding furo[3,4-*d*]pyrimidine-2,5-dione (**8b**, 65%). It is noteworthy that the reaction on the allylic site prevails over a hypothetical aromatic electrophilic amidation process, which would lead to quinolinone **8′**, a compound that was never detected.[15]

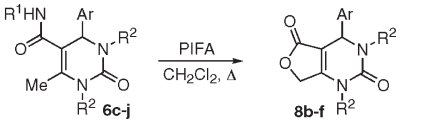
SCHEME 3



6	**8** (%)	Method [a]	R^2	R^3
a	(--) [b]	A-G	H	H
b	**a** (18)	B	H	Me
c	**b** (36)	A	Me	Me
c	**b** (65)	B	Me	Me
c	**b** (25)	C	Me	Me
c	**b** (52)	D	Me	Me
c	**b** (13)	E	Me	Me
c	**b** (51)	F	Me	Me
c	**b** (27)	G	Me	Me

[a] A: TFEA, reflux. B: CH_2Cl_2, reflux. C: BF_3OEt_2 (3 equiv), CH_2Cl_2, rt. D: TFA (3 equiv), CH_2Cl_2, rt. E: TFA (3 equiv), CH_2Cl_2, 0 °C. F: TFA (10 equiv), $CHCl_3$, rt. G: Na_2CO_3 (1.5 equiv), CH_2Cl_2, reflux. [b] A complex mixture of products was obtained in all cases.

SCHEME 4



6	**8** (%)	R^1	Ar	R^2
c	**b** (65)	C_6H_5	m-$MeOC_6H_4$	Me
g	**c** (17)	2,4-diMeC_6H_3	C_6H_5	Me
d	**c** (56)	C_6H_5	C_6H_5	Me
e	**c** (36)	p-$NO_2C_6H_4$	C_6H_5	Me
h	**c** (23)	H	C_6H_5	Me
i	**d** (61)	C_6H_5	2-thienyl	Me
j	**e** (56)	C_6H_5	o-$NO_2C_6H_4$	Me
f	**f** (29)	C_6H_5	m-$MeOC_6H_4$	Et

Once the need for starting from *N*,*N*′-disubstituted ureas and conditions B as the method of choice to perform the projected transformation were established, other structural requirements of the substrates and its extension to different models were analyzed. In particular, the influence of the nature of R^1 will be of interest to obtain some more information about the insights of the reaction. Thus, it was found (see Scheme 4) that regardless of the steric and electronic nature of the amidic *N*-aryl substituent, DHPMs **6c**−**j** rendered the corresponding furo-DHPM **8** on treatment with PIFA although with different efficiency (17−65%). The steric effect results are evident by comparison of the results obtained from **6c**

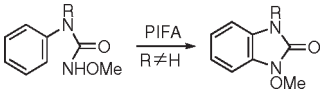
(10) For some illustrating overall views on the C−H activation strategy, see: (a) Bergman, R. G. *Nature* **2007**, *446*, 391−393. (b) Díaz-Requejo, M. M.; Pérez, P. J. *Chem. Rev*. **2008**, *108*, 3379–3394.

(11) As expected to the view of several precedents, the yield for this cyclocondensation is markedly diminished when starting from N,N′-disubstituted ureas. This structural feature will be crucial for our synthetic purposes (vide infra).

(12) For a recent review on heterocyclic synthesis under solvent-free conditions, see: Martins, M. A. P.; Frizzo, C. P.; Moreira, D. N.; Buriol, L.; Machado, P. *Chem. Rev*. **2009**, *109*, 4140–4182.

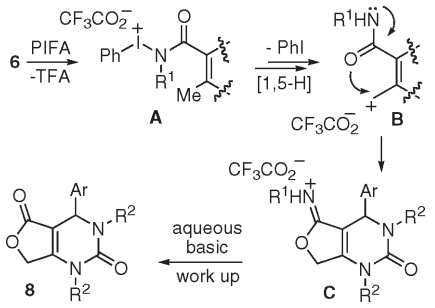
(13) The study was also extended to the use of some other hypervalent iodine reagents (PIDA and IBX), but complex mixtures of compounds were obtained in all cases.

(14) A similar solution was applied in a study related to the intramolecular PIFA-mediated cyclization of *N*-methoxy-*N*′-phenylureas to render 2-benzimidazolinones, which was productive only when an additional *N*′-substituent (R) was incorporated to the starting material. (a) Romero, A. G.; Darlington, W. H.; McMillan, M. W. *J. Org. Chem*. **1997**, *62*, 6582–6587. (b) Romero, A. G.; Darlington, W. H.; Jacobsen, E. J.; Mickelson, J. W. *Tetrahedron Lett*. **1996**, *37*, 2361–2364.



(15) The I(III) mediated intramolecular electrophilic aromatic amidation was first reported by Kikugawa's group and deeply exploited thereafter. Kawase, M.; Kitamura, T.; Kikugawa, Y. *J. Org. Chem*. **1989**, 3394–3403.

SCHEME 5



and **6g**, and also from the fact that a bulkier R^2 substituent (as in **6f**) negatively affects the success of the reaction. On the other hand, the behavior of **6d** with respect to **6e** informs that the presence of deactivated *N*-aryl groups also has a negative influence on the success of the cyclization. It has been found as well that unsubstituted carboxamide **6h** equally produced the expected heterocycle, although in a highly diminished yield (23%).[16] In conclusion, the *N*-phenyl group appears to be the optimal substituent over other activated and deactivated arylic candidates and, therefore, on the basis of these results, the series of furo-DHPMs **8b**,**c** was extended to derivatives **8d**,**e**.

The high dependence of the efficiency of the reaction on the nature of the aryl substituent (R^1) is probably the major informative observation that led us to suggest a plausible mechanism as depicted in Scheme 5. Considering the known ability of PIFA to oxidize amides into nitrenium ions,[17] we propose intermediate **A** as the starting point at which the electronic and steric influence of R^1 in the course of the reaction results is evident. Thus, in view of the transformation of **6d** into **8c**, this assumption explains the diminished efficiency encountered in the preparation of such compounds from **6e**,**g** since, respectively, deactivated *N*-aryl groups (as in **6e**) cannot stabilize the positive charge that is being developed in intermediate **A**, and, on the other hand, hindered arylamides (as in **6g**) hamper the approach of the iodine(III) reagent to the amide. Therefore, *N*-phenyl-substituted substrates appear to be the best selection to accomplish the projected transformation. Then, the ring closure step, which takes place after PhI release, can be explained by a 1,5-hydride shift giving rise to intermediate **B**, in which the allylic position results activated toward the intramolecular nucleophilic attack of the amide group.[18] Apparently, because of its higher nucleophilicity and basicity, it is the oxygen atom, and not the nitrogen, of the amide that promotes the cyclization step to render the iminolactone **C**.[19] Finally, a hydrolysis step during workup renders the final compounds **8**.

In summary, the new reactivity of the iodine(III) reagent PIFA has been developed and extended to a straightforward preparation of furo[3,4-*d*]pyrimidine-2,5-dione derivatives. The present strategy is based on a preliminary preparation of a series of 5-carboxamidodihydropyrimidinones by a Biginelli multicomponent reaction followed by an unprecedented PIFA-mediated intramolecular metal-free allylic oxycarbonylation reaction promoted by the hypervalent iodine reagent that avoids an additional functionalization step of the allylic position.

Experimental Section

Representative Procedure for the Synthesis of Dihydropyrimidine 6a. A mixture of 3-ketoamide **2** (1 mmol), aldehyde **3**(1 mmol), urea **4** (1.5 mmol) and chloroacetic acid (15 mol %) was heated in an oil bath (90 °C) for 7−10 h in the absence of solvents. The progress of the reaction was monitored by TLC. When the reaction was completed, the flask was removed from the oil bath and allowed to stand at room temperature. Then, the mixture was poured into water and extracted with CH_2Cl_2. The organic extracts were dried with Na_2SO_4 (anh), solvent was evaporated under reduced pressure, and the resulting residue was purified by column chromatography (hexanes/EtOAc, 3/7) followed by crystallization from hexanes (65% yield): mp 182−185 °C (hexanes); IR (film) υ 3237, 1682, 1672, 1432; ^{1}H NMR (300 MHz, DMSO-d_6) 2.02 (s, 3H), 3.67 (s, 3H), 5.37 (s, 1H), 6.80−6.85 (m, 2H), 6.96−6.99 (m, 1H), 7.20−7.23 (m, 3H), 7.52−7.55 (m, 3H), 8.68 (br s, 1H), 9.54 (br s, 1H); ^{13}C NMR (300 MHz, DMSO-d_6) 17.5, 55.4, 55.5, 105.8, 112.6, 112.7, 118.7, 120.1, 123.5, 128.9, 130.1, 138.9, 139.7, 149.3, 153.1, 159.7, 165.8; MS [M + 1] *m*/*z* 338 (100), 337 (15), 245 (61), 244 (39); HRMS calcd for $C_{19}H_{19}N_3O_3\cdot H^+$ 338.1517, found 338.1505.

Typical Procedure for the PIFA-Mediated Cyclization Reaction. Synthesis of furoDHPMs 8a−f. A solution of PIFA (1.33 mmol) in CH_2Cl_2 (10 mL) was added to another solution of DHPM **6** (1.0 mmol) in CH_2Cl_2 (5 mL). The new solution was heated to reflux for 5−7 h, and when the reaction was completed, the mixture was cooled to room temperature then washed with 10% aq Na_2CO_3 (1 × 10 mL) and brine (1 × 10 mL). The organic phase was dried on Na_2SO_4 and filtered, and the solvent was removed under reduced pressure. The resulting residue was purified as indicated for each individual compound.

Synthesis of 4-(3-Methoxyphenyl)-1-methyl-4,7-dihydro-1*H*,3*H*-furo[3,4-*d*]pyrimidine-2,5-dione (8a). According to the typical procedure furoDHPM **8a** was obtained from DHPM **6b** in 18% yield as a yellowish solid after purification by column chromatography (hexanes/EtOAc, 3/7) followed by crystallization from hexanes: mp 126−129 °C (hexanes); IR (film) υ 1751, 1315; ^{1}H NMR (300 MHz, $CDCl_3$) 3.13 (s, 3H), 3.78 (s, 3H), 4.76 (s, 2H), 5.37 (s, 1H), 5.80 (s, 1H), 6.72−6.81 (m, 3H), 7.24−7.29 (m, 1H); ^{13}C NMR (300 MHz, $CDCl_3$) 29.9, 53.7, 55.3, 64.6, 99.2, 112.1, 113.9, 118.3, 130.0, 142.4, 151.4, 158.7, 160.3, 169.6; MS [M + 1] *m*/*z* 275 (100), 274 (21), 273 (52), 167 (23); HRMS calcd for $C_{14}H_{14}N_2O_4\cdot H^+$ 275.1032, found 275.1028.

Synthesis of 4-(3-Methoxyphenyl)-1,3-dimethyl-4,7-dihydro-1*H*,3*H*-furo[3,4-*d*]pyrimidine-2,5-dione (8b). According to the typical procedure furoDHPM **8b** was obtained from DHPM **6c** in 65% yield as a yellowish solid after purification by column chromatography (hexanes/EtOAc, 1/1) followed by crystallization from hexanes: mp 205−210 °C (hexanes); IR (film) υ 1712, 1328; ^{1}H NMR (300 MHz, $CDCl_3$) 2.90 (s, 3H), 3.17 (s, 3H),

(16) A Hofmann rearrangement leading to a 5-aminoDHPM was not observed either.

(17) Aryl groups were selected, over other possibilities, on the basis of their known ability to stabilize oxidized amides (acylnitrenium ions). See, for example: (a) Falvey, D. E. In *Reactive Intermediate Chemistry*; Moss, R. A., Platz, M., Jones, M., Jr., Eds.; John Wiley & Sons: Hoboken, NJ, 2004; pp 593−650 and references cited therein. (b) Malamidou-Xenikaki, E.; Spyroudis, S.; Tsanakopoulou, M.; Hadjipavlou-Litina, D. *J. Org. Chem.* **2009**, *74*, 7315–7321. (c) Kikugawa, Y. *Heterocycles* **2009**, *78*, 571–607.

(18) Metal-catalyzed C−H activation processes accomplished as a result of the generation of stabilized deficient intermediates followed by a 1,5-hydride shift are known. See, for example: (a) Tobisu, M.; Chatani, N. *Angew. Chem., Int. Ed.* **2006**, *45*, 1683–1684. (b) Tobisu, M.; Nakai, H.; Chatani, N. *J. Org. Chem.* **2009**, *74*, 5471.

(19) This particular behavior, in the context of I(III)-mediated heterocyclic synthesis, was first reported by Kita's group. (a) Tamura, Y.; Yakura, T.; Haruta, J.-I.; Kita, Y. *J. Org. Chem.* **1987**, *52* (2), 3927–3930. Later, the preferential formation of lactams over lactones was reached by subtle modification of the amide functional group by Knappp's and Ciufolini's groups: (b) Knapp, S.; Levorse., A. T. *J. Org. Chem.* **1988**, *53*, 4006–4014. (c) Braun, N. A.; Ousmer, M.; Bray, J. D.; Bouchu, B.; Peters, K.; Peters, E.-M.; Ciufolini, M. A. *J. Org. Chem.* **2000**, *65*, 4397–4408.

3.80 (s, 3H), 4.75 (s, 2H), 5.21 (s, 1H), 6.83−6.89 (m, 3H), 7.26−7.32 (m, 1H); ^{13}C NMR (300 MHz, $CDCl_3$) 30.7, 34.8, 55.3, 60.4, 64.5, 98.6, 112.3, 113.6, 118.5, 130.1, 140.5, 151.8, 158.1, 160.1, 169.5; MS [M + 1] *m*/*z* 289 (100), 288 (34), 181 (71); HRMS calcd for $C_{15}H_{16}N_2O_4 \cdot H^+$ 289.1188, found 289.1192.

Synthesis of 1,3-Dimethyl-4-phenyl-4,7-dihydro-1*H*,3*H*-furo-[3,4-*d*]pyrimidine-2,5-dione (8c). According to the typical procedure furoDHPM **8c** was obtained from DHPMs **6d**,**e**,**g**,**h** in 56%, 36%, 17%, and 23% yield, respectively, as a yellowish oil after purification by column chromatography (hexanes/EtOAc, 1/1): IR (film) *v* 1714, 1221; ^{1}H NMR (300 MHz, $CDCl_3$) 2.89 (s, 3H), 3.20 (s, 3H), 477 (s, 2H), 5.21 (s, 1H), 7.24−7.41 (m, 5H); ^{13}C NMR (300 MHz, $CDCl_3$) 30.6, 34.8, 60.5, 64.5, 98.5, 126.3, 128.6, 129.1, 138.9, 152.0, 158.0, 169.4; MS [M + 1] *m*/*z* 259 (100), 258 (23), 181 (78); HRMS calcd for $C_{14}H_{14}N_2O_3 \cdot H^+$ 259.1083, found 259.1097.

Synthesis of 1,3-Dimethyl-4-(2-thienyl)-4,7-dihydro-1*H*,3*H*-furo[3,4-*d*]pyrimidine-2,5-dione (8d). According to the typical procedure furoDHPM **8d** was obtained from DHPM **6i** in 61% yield as a yellowish solid after purification by column chromatography (hexanes/EtOAc, 2/8) followed by crystallization from hexanes: mp 234−240 °C (hexanes); IR (film) *v* 2926, 1685, 1440; ^{1}H NMR (300 MHz, $CDCl_3$) 2.97 (s, 3H), 3.19 (s, 3H), 4.78 (d, J = 15.7, 1H), 4.84 (d, J = 15.7, 1H), 5.54 (s, 1H), 7.06−7.28 (m, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) 30.9, 34.7, 55.9, 64.5, 98.3, 126.3, 126.4, 127.0, 137.1, 139.9, 142.7, 158.1, 169.2; MS [M + 1] *m*/*z* 265 (48), 264 (35), 181 (100); HRMS calcd for $C_{12}H_{12}N_2O_3S \cdot H^+$ 265.0647, found 265.0656.

Synthesis of 1,3-Dimethyl-4-(*o*-nitrophenyl)-4,7-dihydro-1*H*,-3*H*-furo[3,4-*d*]pyrimidine-2,5-dione (8e). According to the typical procedure furoDHPM **8e** was obtained from DHPM **6j** in 56% yield as a yellowish solid after purification by column chromatography (hexanes/EtOAc, 2/8) followed by crystallization from hexanes: mp 176−180 °C (hexanes); IR (film) *v* 1751, 1320; ^{1}H NMR (300 MHz, $CDCl_3$) 2.90 (s, 3H), 3.19 (s, 3H), 4.77 (s, 2H), 6.24 (s, 1H), 6.66−6.69 (m, 1H), 7.14−7.18 (m, 1H), 7.43−7.55 (m, 1H), 7.85−7.90 (m, 1H); ^{13}C NMR (300 MHz, $CDCl_3$) 30.7, 34.8, 55.9, 64.5, 97.3, 115.2, 125.0, 129.3, 133.4, 133.5, 148.8, 151.6, 158.5, 168.8; MS [M + 1] *m*/*z* 304 (100), 286 (31), 273 (52), 181 (42).

Synthesis of 1,3-Diethyl-4-(3-methoxyphenyl)-4,7-dihydro-1*H*,3*H*-furo[3,4-*d*]pyrimidine-2,5-dione (8f). According to the typical procedure furoDHPM **8f** was obtained from DHPM **6f** in 29% yield as a yellowish solid after purification by column chromatography (hexanes/EtOAc, 3/7) followed by crystallization from hexanes: mp 110−115 °C (hexanes); IR (film) *v* 1742, 1334; ^{1}H NMR (300 MHz, $CDCl_3$) 1.16−1.29 (m, 6H), 2.81−2.92 (m, 1H), 3.43−3.56 (m, 1H), 3.63−3.86 (m, 5H), 4.75 (s, 2H), 5.28 (s, 1H), 6.76−6.81 (m, 3H), 7.26−7.32 (m, 1H); ^{13}C NMR (300 MHz, $CDCl_3$) 12.2, 14.6, 39.6, 41.8, 55.3, 57.5, 64.5, 99.9, 112.2, 113.7, 118.6, 130.2, 141.4, 160.1, 157.5, 160.1, 169.7; MS [M + 1] *m*/*z* 317 (100), 316 (31), 273 (21), 209 (31); HRMS calcd for $C_{17}H_{20}N_2O_4 \cdot H^+$ 317.1501, found 317.1482.

Acknowledgment. Financial support from the University of the Basque Country and Basque Government (GIU 06/87) and the Spanish Ministry of Education and Science (CTQ2007-64501/BQU) is gratefully acknowledged. I.C. thanks the Ministry of Science and Technology for a predoctoral scholarship.

Supporting Information Available: Characterization data and copies of NMR spectra for compounds **6a**−**j** and **8a**−**f**. This material is available free of charge via the Internet at http://pubs.acs.org.