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An Efficient Synthesis of Hydantoins via Sustainable Integration of Coupled Domino Processes

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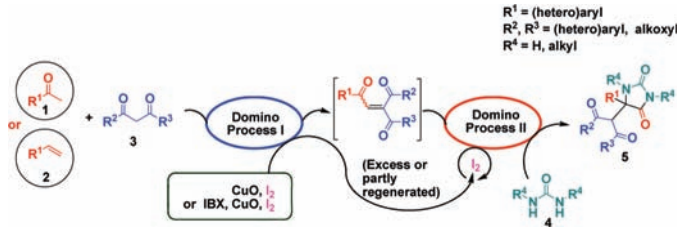
ABSTRACT



A highly efficient synthesis of hydantoins has been developed from simple and commercially available 1,3-dicarbonyl compounds, ureas, and methyl ketones or terminal aryl alkenes. This protocol involves a sustainable integration of two coupled domino processes: iodine-promoted synthesis of unsymmetrical 1,4-enediones (domino I) and the sequential transformation into hydantoins (domino II).

In modern synthetic chemistry, a growing trend toward the integration of discrete reactions in one process has been well illustrated by domino reactions[1] and one-pot multicomponent reactions,[2] which allow the direct synthesis of complex molecules from simple substrates in a highly efficient manner. A particularly attractive domino strategy is that which involves a multiple use of catalysts or reagents to promote mechanistically distinct processes. For example, the "autotandem catalysis" strategy involves a catalyst to catalyze two or more distinct chemical transformations in a single flask.[3] However, as many important reactions still need "stoichiometric" reagents to guarantee their efficiency,[4] new strategies are urgent and important to improve the atom efficiency of such reactions. During the past few years, a chain of two or more coupled domino processes has been linked in a one-pot operation, which is a very convenient approach to complex architectures via a multiplicative effect.[5] In this context, we hypothesized that a multiuseful reagent could be used to promote both "stoichiometric" and "catalytic" domino processes in a one-pot reaction for maximizing synthetic efficiency.

Recently, a sustainable synthetic strategy has been proposed to allow the byproducts of a stoichiometric reaction to be internally recycled to catalyze the subsequent reaction

(1) For reviews on domino reactions, see: (a) Tietze, L. F.; Brasche, G.; Gericke, K. *Domino Reactions in Organic Synthesis*; Wiley-VCH: Weinheim, Germany, 2006. (b) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115. (c) Nicolaou, K. C.; Montagnon, T.; Snyder, S. A. *Chem. Commun.* **2003**, 551.

(2) For reviews on multicomponent reactions, see: (a) Zhu, J. P., Bienaymé, H., Eds.; *Multicomponent Reactions*; Wiley-VCH: Weinheim, 2005. (b) Ramón, D. J.; Yus, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 1602. (c) Simon, C.; Constantieux, T.; Rodriguez, J. *Eur. J. Org. Chem.* **2004**, 4957.

(3) For reviews on the "autotandem catalysis" strategy, see: (a) Shindoh, N.; Takemoto, Y.; Takasu, K. *Chem.—Eur. J.* **2009**, *15*, 12168. (b) Wasilke, J. C.; Obrey, S. J.; Baker, R. T.; Bazan, G. C. *Chem. Rev.* **2005**, *105*, 1001. (c) Fogg, D. E.; dos Santos, E. N. *Coord. Chem. Rev.* **2004**, *248*, 2365.

(4) For selected examples in carbon−carbon double bond formation using "stoichiometric" reagents, see the Wittig reaction, Peterson olefination, Julia olefination, Mcmurry reaction, and Tebbe olefination.

(5) (a) Tejedor, D.; González-Cruz, D.; García-Tellado, F.; Marrero-Tellado, J. J.; Rodríguez, M. L. *J. Am. Chem. Soc.* **2004**, *126*, 8390. (b) Yamamoto, Y.; Hayashi, H.; Saigoku, T.; Nishiyama, H. *J. Am. Chem. Soc.* **2005**, *127*, 10804.

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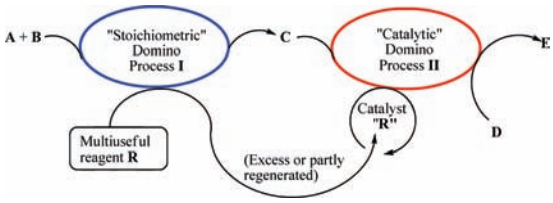
in a domino process.[6] For example, Alaimo et al. first demonstrated the power of this strategy in a domino nitroarene reduction/imine formation/aza Diels−Alder reaction, which utilized the In^{III} byproducts generated in the reduction step to catalyze the aza-Diels−Alder reaction.[6a] Inspired by this excellent strategy and with our interests in exploring multiuseful reagents to promote coupled domino processes, we reported here a novel sustainable strategy, which involves a multiuseful reagent to promote the upstream stoichiometric domino reaction, and the excess or partly regenerated reagent could be internally recycled to catalyze the downstream catalytic domino reaction (Scheme 1).

Scheme 1. Sustainable Integration of Coupled Domino Processes[a]

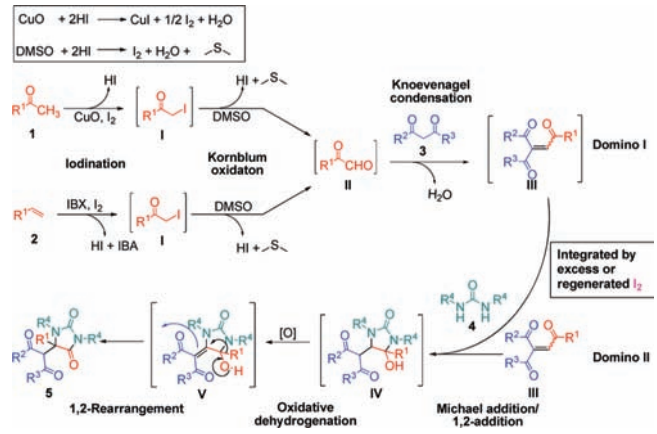


[a] In the first domino process, multiuseful reagent **R** could promote the reaction of substrates **A** and **B** to give intermediate **C**, and then the excess or partly regenerated reagent "**R**" is internally recycled to catalyze the second domino reaction of intermediate **C** with reactant **D** to afford final product **E**.

Because of the pharmacological importance of hydantoins,[7] their efficient and elegant synthesis would be an ideal testing ground for demonstrating the power and potential of this strategy. Especially, as there were only very few methods for the direct synthesis of bioactive 1,3,5,5-tetrasubstituted hydantoins,[8] a straightforward and practical methodology is highly desirable for their synthesis.

In our previous studies, a focusing domino reaction was proposed to synthesize unsymmetrical 1,4-enediones from 1,3-dicarbonyl compounds and methyl ketones or terminal aryl alkenes in the presence of a stoichiometric CuO/I_2 or $IBX/CuO/I_2$.[9] In this domino process, hydrogen iodide was generated as a byproduct in the iodination and Kornblum oxidation step, which could be oxidized by CuO or DMSO to regenerate at least 0.5 equiv of iodine (see Scheme 2).[10]

Scheme 2. Proposed Reaction Pathway



On the basis of this facile access to unsymmetrical 1,4-enediones, a potentially useful approach was proposed in Scheme 2 for the synthesis of hydantoins. It is expected that a consecutive Michael addition and 1,2-addition of dinucleophilic ureas to unsymmetrical 1,4-enediones **III** would provide the five-membered cyclic intermediate **IV**, which would then undergo oxidative dehydrogenation[11] and 1,2-rearrangement[12] to afford the hydantoins **5**.

Considering oxidative conditions would be necessary for the proposed domino process **II**, various oxidants were first explored using the 1,4-enedione **IIIa** and 1,3-dimethyl urea **4a** as substrates, with a goal of identifying reaction conditions compatible with the previous domino process (Table 1). Fortunately, the expected hydantoin **5a** was obtained in 15% isolated yield in the presence of 10 mol % of I_2 at 100 °C, which was unambiguously confirmed by X-ray diffraction.[13] Much to our satisfaction, by increasing the catalyst loading to 0.5 equiv, hydantoin **5a** was obtained in 93% yield after 3 h (Table 1, entry 3).[14] The presence of I_2 is important for

(6) (a) Alaimo, P. J.; O'Brien, R.; Johnson, A. W.; Slauson, S. R.; O'Brien, J. M.; Tyson, E. L.; Marshall, A.-L.; Ottinger, C. E.; Chacon, J. G.; Wallace, L.; Paulino, C. Y.; Connell, S. *Org. Lett.* **2008**, *10*, 5111. (b) Yang, B.-L.; Weng, Z.-T.; Yang, S.-J.; Tian, S.-K. *Chem.—Eur. J.* **2010**, *16*, 718. (c) Cao, J.-J.; Zhou, F.; Zhou, J. *Angew. Chem., Int. Ed.* **2010**, *49*, 4976.

(7) Reviews: (a) Meusel, M.; Gutschow, M. *Org. Prep. Proced. Int.* **2004**, *36*, 391. (b) Ware, E. *Chem. Rev.* **1950**, *46*, 403. (c) López, C. A.; Trigo, G. G. *Adv. Heterocycl. Chem.* **1985**, *38*, 177. (d) Volonterio, A.; Zanda, M. *Tetrahedron Lett.* **2003**, *44*, 8549.

(8) For examples of pharmaceutical research on tetrasubstituted hydantoins, see: (a) Last-Barney, K.; Davidson, W.; Cardozo, M.; Frye, L. L.; Grygon, C. A.; Hopkins, J. L.; Jeanfavre, D. D.; Pav, S.; Qian, C.; Stevenson, J. M.; Tong, L.; Zindell, R.; Kelly, T. A. *J. Am. Chem. Soc.* **2001**, *123*, 5643. For synthesis of tetrasubstituted hydantoins, see: (b) Moskal, J.; Moskal, A. *Synthesis* **1979**, 794. (c) Moskal, J.; Moskal, A.; Milart, P. *Monatsh. Chem.* **1984**, *115*, 187. (d) Meusel, M.; Ambrožak, A.; Hecker, T. K.; Gutschow, M. *J. Org. Chem.* **2003**, *68*, 4684. (e) Alizadeh, A.; Bijanzadeh, H. R. *Synthesis* **2004**, 3023.

(9) Gao, M.; Yang, Y.; Wu, Y.-D.; Deng, C.; Cao, L.-P.; Meng, X.-G.; Wu, A.-X. *Org. Lett.* **2010**, *12*, 1856.

(10) (a) Yin, G.; Zhou, B.; Meng, X.; Wu, A.; Pan, Y. *Org. Lett.* **2006**, *8*, 2245. (b) Yin, G.; Wang, Z.; Chen, A.; Gao, M.; Wu, A.; Pan, Y. *J. Org. Chem.* **2008**, *73*, 3377. (c) Gao, M.; Yin, G. D.; Wang, Z. H.; Wu, Y. D.; Guo, C.; Pan, Y. J.; Wu, A. X. *Tetrahedron* **2009**, *65*, 6047. (d) Yin, G.; Gao, M.; She, N.; Hu, S.; Wu, A.; Pan, Y. *Synthesis* **2007**, 3113.

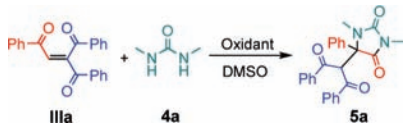
(11) For reviews of oxidative dehydrogenation adjacent to carbonyl functionalities, see: (a) Kleinman, E. F. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Heathcock, C. H., Eds.; Pergamon Press: Oxford, U.K., 1991; Vol. 7, pp 119−146. (b) Sommer, T. J. *Synthesis* **2004**, 161. (c) Nicolaou, K. C.; Montagnon, T.; Baran, P. S.; Zhong, Y. L. *J. Am. Chem. Soc.* **2002**, *124*, 2245.

(12) For review on 1,2-rearragement, see :(a) Brückner, R. In *Advanced Organic Chemistry: Reaction Mechanisms*; Harcourt/Academic Press: San Diego, 2002; pp 435−476. For selected examples in synthesis of hydantoins involving 1,2-rearrangement reactions, see: (b) Muccioli, G. G.; Poupaert, J. H.; Wouters, J.; Norberg, B.; Poppitz, W.; Scriba, G. K. E.; Lambert, D. M. *Tetrahedron* **2003**, *59*, 1301. (c) Paul, S.; Gupta, M.; Gupta, R.; Loupy, A. *Synthesis* **2002**, 75.

(13) CCDC 773974 (**5a**) and 777267 (**8**) contain the supplementary crystallographic data for this paper.

(14) Iodine acts as a oxidation catalyst in domino process **II**, as its reduction product HI could be oxidized by DMSO to regenerate iodine (see Scheme 2).

Table 1. Optimization of the Reaction Conditions for Domino **II**[a]



entry	oxidant	equiv	t (h)	temp (°C)	yield (%)[b]
1	I_2	0.1	6	100	15
2	I_2	0.3	6	100	56
3	I_2	0.5	3	100	93
4	I_2	0.5	6	70	0
5	I_2	1.0	6	70	0
6	none	-	6	100	0
7	CuO	1.0	6	100	0
8	DDQ	1.0	6	100	68
9	IBX	1.0	6	100	51
10	PIDA	1.0	6	100	0
11	SeO_2	1.0	6	100	45
12	$Mn(OAc)_3{\cdot}2H_2O$	1.0	6	100	0
13	TEMPO	1.0	6	100	0
14	H_2O_2	1.0	6	100	74

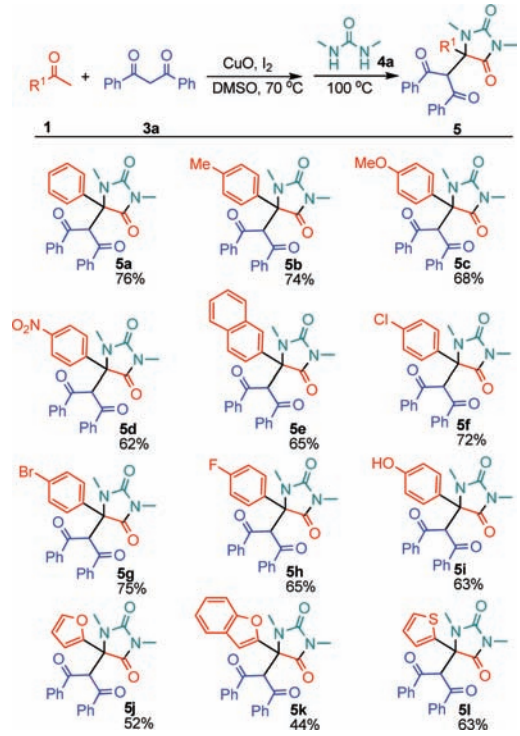
[a] Reaction conditions: **IIIa** (0.2 mmol), **4a** (0.4 mmol) in 1 mL of DMSO under an atmosphere of argon. [b] Isolated yields. DDQ = 2,3-dichloro-5,6-dicyanobenzoquinone; IBX = 2-iodoxybenzoic acid; PIDA = iodosobenzene diacetate; TEMPO = 2,2,6,6-tetramethyl-piperidine-1-oxyl.

accelerating equilibrium toward the hydantoins; otherwise, a mixture of products would be obtained (Table 1, entry 5).[15] Employing other oxidants under this condition failed to produce better results (Table 1, entries 6−13).

Encouraged by the discovery that iodine could promote both domino processes and it could be regenerated in domino process **I**, we wondered whether it would be possible to prepare hydantoins via an integration of the two coupled domino processes in a one-pot reaction (see Scheme 2). After some optimization studies, the feasibility of this strategy was verified by reaction of 1.0 mmol of acetophenone **1a** and 1.0 mmol of 1,3-diphenylpropane-1,3-dione **3a** in the presence of 1.1 mmol of CuO and 1.1 mmol of iodine in 5 mL of DMSO under an atmosphere of argon at 70 °C for 12 h. After the substrates were completely consumed, 2.0 mmol of 1,3-dimethyl urea **4a** was added, and the reaction mixture was stirred at 100 °C for 3 h. After workup, the desired hydantoin **5a** was obtained in 76% yield (Scheme 3), which is comparable to the stepwise reaction.[16]

With this optimized result in hand, we next explored the scope of this reaction. Pleasingly, all methyl ketones, regardless of their electronic or steric properties, proceeded efficiently to afford their corresponding products in moderate to good yields (44−76%; Scheme 3). For example, electron-neutral (H, CH_3), electron-rich (OCH_3), electron-deficient (NO_2), and sterically hindered (β-naphthyl) methyl ketones all reacted efficiently to give the expected hydantoins in excellent yields (62−76%; **5a**−**5e**). Much to our satisfaction, good yields were obtained with halogenated and hydroxylated substrates (63−75%; **5f**−**5i**). The heteroaryl methyl ketones could also give their corresponding products in moderate yields (44−63%; **5j**−**5l**). However, use of unsaturated methyl ketones was unsuccessful.[17]

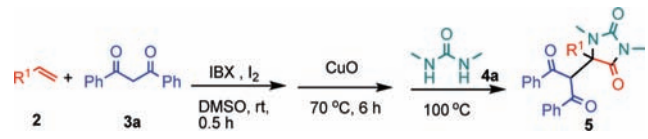
Scheme 3. Scope of Methyl Ketones[a]



[a] Reaction was performed with methyl ketone **1** (1.0 mmol), **3a** (1.0 mmol), CuO (1.1 mmol), and I_2 (1.1 mmol) in DMSO (5 mL) at 70 °C for 12 h; then, **4a** (2.0 mmol) was added, and the mixture was stirred at 100 °C for another 3−4 h. Yield of the isolated product shown.

To our delight, terminal aryl alkenes could also smoothly react with **3a** and **4a** to give the desired products (Table 1). The steric and electronic nature of the alkenes had little influence on the reaction efficiency, and generally good yields were obtained (56−68%; Table 2).

Table 2. Scope of Terminal Aryl Alkenes[a]



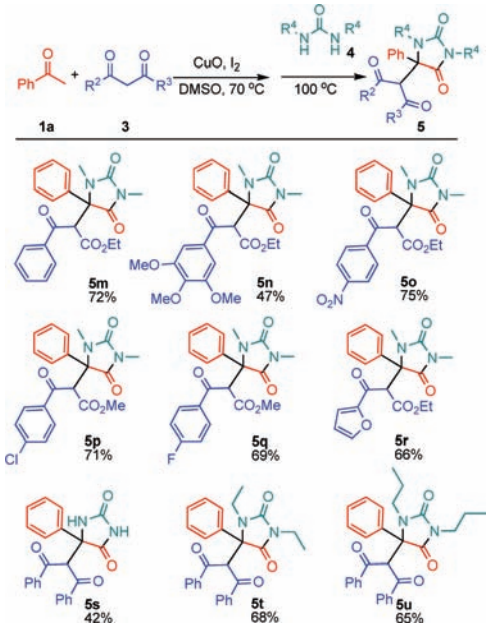
entry	**2** (R^1)	**5**	yield (%)[b]
1	**2a** (C_6H_5)	**5a**	68
2	**2b** (4-MeC_6H_4)	**5b**	65
3	**2c** (4-$MeOC_6H_4$)	**5c**	56
4	**2d** (β-naphthyl)	**5e**	62
5	**2e** (4-ClC_6H_4)	**5f**	63
6	**2f** (4-BrC_6H_4)	**5g**	65
7	**2g** (4-FC_6H_4)	**5h**	59

[a] Reaction was performed with terminal aryl alkene **2** (1.0 mmol), IBX (1.2 mmol), and I_2 (1.1 mmol) in DMSO (5 mL) at room temperature for 0.5 h; then **3a** (1.0 mmol) and CuO (1.1 mmol) were added; and the mixture was stirred at 70 °C for 6 h. After the substrates were completely consumed, **4a** (2.0 mmol) was added, and the mixture was stirred at 100 °C for another 3−4 h. [b] Isolated yield.

(15) The ^{1}H NMR of the crude reaction mixture showed that the hydantoin **5a** was not included in the mixture.

(16) The isolated yield for the 1,4-enedione **IIIa** was 84%, and the overall yield for the hydantoin **5a** was 78% via stepwise reaction.

Scheme 4. Scope of 1,3-Dicarbonyl Compounds and Ureas[a]

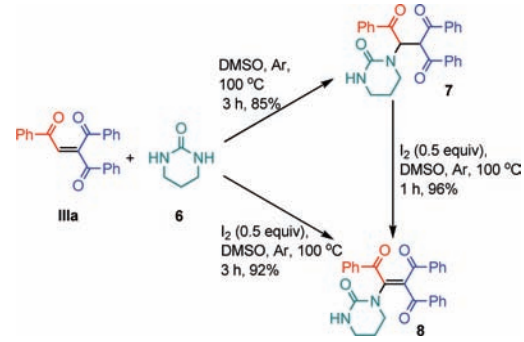


[a] Reaction conditions: see Scheme 3 or the Supporting Information. Yield of the isolated product shown.

Using acetophenone, structural variations in the 1,3-dicarbonyl compounds and ureas were then examined (Scheme 4). In the case of electron-neutral (H) and electron-deficient (NO_2) 1,3-dicarbonyl compounds, a satisfactory yield was obtained (72%, 75%; **5m**, **5o**). However, when strong electron-donating groups were attached to the phenyl ring of the 1,3-dicarbonyl compounds, the yield dropped obviously (47%; **5n**). Significantly, halogen and the heterocycle containing 1,3-diketones were readily tolerated in this transformation (66−71%; **5p**−**5r**).[18] Unfortunately, use of aliphatic 1,3-dicarbonyl compounds was unsuccessful, which led to a mixture of products.[19] To our delight, various urea derivatives could also complete this transformation. Although urea gave its corresponding product in a lower yield (42%; **5s**), 1,3-diethyl urea and 1,3-dipropyl urea could give their corresponding products in good yields (65−68%; **5t**−**5u**).

To provide insight into the oxidative dehydrogenation step in domino process **II**, a control experiment was performed (Scheme 5). When 1,4-enedione **IIIa** was treated with tetrahydropyrimidin-2-one **6** in the presence of 0.5 equiv of I_2 in DMSO under argon at 100 °C for 3 h, product **8** was obtained in 92% yield, which was unambiguously confirmed by X-ray diffraction.[13] When the reaction was conducted without iodine, only Michael addition product **7** was obtained in 85% yield after 3 h, which could be further oxidized by

Scheme 5. Control Experiment[a]



[a] Reaction conditions: see the Supporting Information. Yield of the isolated product shown.

I_2 to give compound **8** in 96% yield within 1.0 h. This result clearly confirmed our suspicion that I_2 could efficiently catalyze the oxidative dehydrogenation step.

In summary, we have developed a sustainable integration of double domino processes for the straightforward construction of tetrasubstituted hydantoins. It comprises six mechanistically different reactions: iodination−Kornblum oxidation−Knoevenagel condensation−dinucleophilic addition−oxidative dehydrogenation−1,2-rearrangement reaction. The easy generation of molecular diversity along with the importance of tetrasubstituted hydantoins in medicinal chemistry makes the reaction described here an appropriate protocol for the synthesis of potentially bioactive compounds. Further investigation into the reaction mechanism and application of this strategy are currently underway in our laboratory.

Acknowledgment. We thank the National Natural Science Foundation of China (Grant 20872042, 20902035 and 21032001).

Supporting Information Available: Experimental procedures and compound characterization data including X-ray crystal data for **5a** and **8**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) Unsaturated methyl ketones tested include (*E*)-4-phenylbut-3-en-2-one, (*E*)-4-(4-methoxyphenyl)but-3-en-2-one, (*E*)-4-(4-nitrophenyl)but-3-en-2-one, and (3*E*,5*E*)-6-phenylhexa-3,5-dien-2-one.

(18) Compounds **5m**−**5r** were obtained as a mixture of two racemic diastereoisomers, while compounds **5a**−**5l** and **5s**−**5u** were obtained as a racemic mixture. For more details, see the Supporting Information.

(19) Aliphatic 1,3-dicarbonyl compounds tested include pentane-2,4-dione and ethyl 3-oxobutanoate.