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Selective Formation of Spiro Dihydrofurans and Cyclopropanes Through Unexpected Reaction of Aldehydes with 1,3-Dicarbonyl Compounds

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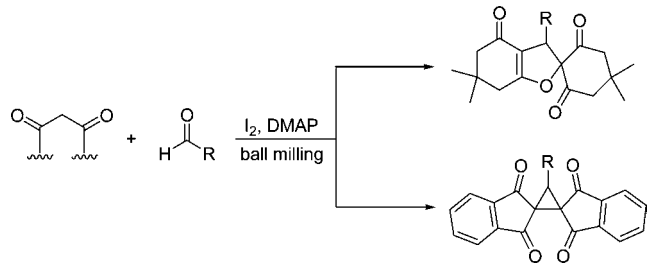
ABSTRACT



An efficient methodology for the oxidative addition reaction of various aldehydes with 5,5-dimethylcyclohexane-1,3-dione and 1,3-indandione to selectively afford spiro dihydrofuran and cyclopropane derivatives, promoted by molecular iodine and dimethylaminopyridine under mechanical milling conditions, has been demonstrated. The products were obtained in good to excellent yields. A possible mechanism of this unusual reaction process is proposed.

Substituted dihydrofurans occur frequently in numerous natural compounds, showing important biological activities and wide applications in pharmaceutical use.[1] Due to their important use in organic synthesis, the synthetic methodologies for dihydrofurans have been studied for many years. Dimroth and Pasedach presented a methodology to synthesize 2,3-dihydrofurans from the dehydration of 1,4-diols under high temperature and pressure conditions.[2] The intramolecular cyclization of alkynyl alcohols to generate 2,3-dihydrofurans was realized by the promotion of a pentacarbonylmolybdenum/triethylamine complex.[3] The dihydrofuran moiety could also be constructed by Rh-catalyzed reactions of diazo compounds or iodonium ylides with alkenes.[4] More commonly, oxidative cyclization of active methylene compounds with alkenes by metal salts, such as manganese(III) acetate and cerium(IV) ammonium nitrate, to generate the requisite dihydrofuran motif received considerable attention.[5]

Cyclopropane rings are also ubiquitous in biologically active compounds.[6] The construction of cyclopropane rings

(1) (a) *The Chemistry of Heterocycles: Structure, Reactions, Syntheses, and Applications*; Eicher, T., HauptmannS. Eds.; Wiley-VCH: Weinheim, 2003. (b) Lipshutz, B. H. *Chem. Rev.* **1986**, *86*, 795.

(2) Dimroth, P.; Pasedach, H. *Angew. Chem.* **1960**, *22*, 865.

(3) Mcdonald, F. E.; Connolly, C. B.; Gleason, M. M.; Towne, T. B.; Treiber, K. D. *J. Org. Chem.* **1993**, *58*, 6952.

(4) (a) Pirrung, M. C.; Blume, F. *J. Org. Chem.* **1999**, *64*, 3642. (b) Lee, Y. R.; Suk, J. Y. *Tetrahedron* **2002**, *58*, 2359. (c) Lee, Y. R.; Hwang, J. C. *Eur. J. Org. Chem.* **2005**, 1568.

(5) (a) Hwu, J. R.; Chen, C. N.; Shiao, S.-S. *J. Org. Chem.* **1995**, *60*, 856. (b) Nishino, H.; Nguyen, V.-H.; Yoshinaga, S.; Kurosawa, K. *J. Org. Chem.* **1996**, *61*, 8264. (c) Garzino, F.; Méou, A.; Brun, P. *Tetrahedron Lett.* **2000**, *41*, 9803. (d) Burgaz, E. V.; Yilmaz, M.; Pekel, A. T.; ÖKtemer, A. *Tetrahedron* **2007**, *63*, 7229. (e) Wang, G.-W.; Dong, Y.-W.; Wu, P.; Yuan, T.-T.; Shen, Y.-B. *J. Org. Chem.* **2008**, *73*, 7088.

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is of great importance for their intrinsic utility of key intermediates for further transformations.[7] Among the existing methods for cyclopropanation reactions, the Simmons−Smith-type reaction is probably the most widely used.[8] The iodine and Lewis acid-mediated intramolecular cyclopropanation reaction of unsaturated β-keto esters has been reported.[9] Metal-catalyzed cyclopropanation of alkenes with diazo compounds has also attracted much attention recently.[10] However, these reported procedures often required severe reaction conditions or heavy metal catalysts. A methodology with smooth reaction conditions and a metal-free reaction process is rather rare and highly desirable.

As an inexpensive, efficient, and environmentally benign reagent, molecular iodine has been used extensively in organic synthesis for a long time. In recent years, more and more organic transformations mediated by molecular iodine have been documented.[11]

On the other hand, solvent-free organic reactions, which supply environmentally friendly protocols and sometimes remarkable reaction acceleration and more convenient product purification, have drawn the public's concerns increasingly in recent years. The mechanical milling technique is a powerful tool to promote solvent-free reactions.[12−14] In light of our successful studies in this field,[5e,13] herein we present the unexpected reaction of aldehydes with 1,3-dicarbonyl compounds promoted by iodine and DMAP under mechanical ball-milling conditions as a novel and green protocol to produce dihydrofuran and cyclopropane derivatives in good yields.

At the outset of our studies, we attempted to find a feasible pathway to pyran formation under our mechanical milling conditions. In an initial experiment, a mixture of 5,5-dimethylcyclohexane-1,3-dione (dimedone) (**1**), 3-nitrobenzaldehyde (**2a**), dimethylaminopyridine (DMAP), and molecular iodine in a molar ratio of 2:1:2.5:1.5 was introduced into a stainless jar (5 mL), together with a stainless ball of 7.0 mm diameter, the same mixture was also introduced into a second parallel jar. The two reaction vessels were closed and fixed on the vibration arms of a ball-milling apparatus (Retsch MM200 mixer mill, Retsch GmbH, Haan, Germany) and were vibrated vigorously at a rate of 1800 rounds per minute (30 Hz) at room temperature for 60 min.[13]

After simple workup, one main product was isolated in a low yield. However, the NMR spectra of this compound were not consistent with the pyran structure. Further analysis of the NMR spectra revealed that this compound might contain a dihydrofuran framework. Finally, the structure was unequivocally established by the X-ray diffraction of its single crystal (Figure 1). The formation of a spiro dihydrofuran

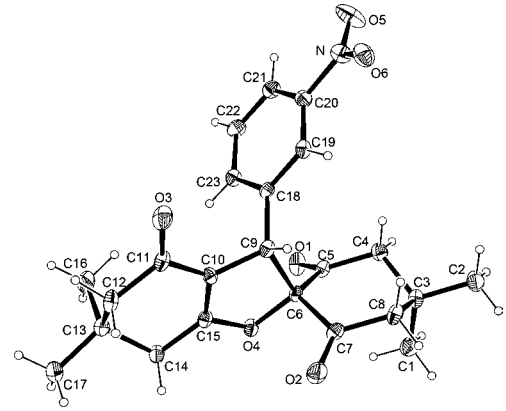


Figure 1. X-ray crystal structure of **3a**.

structure is very unusual and may find its application in related transformations leading to useful products. Encouraged by this unexpected result, we further optimized the reaction conditions by employing various additives. The results are listed in Table 1. With 1.65 equiv of molecular iodine and 2.5 equiv of DMAP as the additives, 3-nitrobenzaldehyde was able to react with 2.4 equiv of dimedone to afford dihydrofuran product **3a** in high yield (91%, entry 1). Other halogen sources such as CBr_4, NBS, NCS, and the combination of Oxone and NaBr were also screened. However, all of them gave the final product in low to moderate yields (entries 2−5). The Oxone/$ZnCl_2$ system failed to give any product (entry 6). Then the effect of various bases was investigated. Only a trace amount of **3a** was observed when $NaHCO_3$ and Na_2CO_3 were employed (entries 7 and 8). Other organic and inorganic bases including Cs_2CO_3, K_2CO_3, DABCO, and DBU facilitated the reaction to some extent, but none exceeded the result of DMAP (entries 9−12). Therefore, this reaction was most efficient when using I_2 (1.65 equiv) and DMAP (2.5 equiv).

With the optimized conditions in hand, the scope and generality of the reaction was explored. A variety of

(6) Wessjohann, L. A.; Brandt, W.; Thiemann, T. *Chem. Rev.* **2003**, *103*, 1625.

(7) (a) Wong, H. N. C.; Hon, M.-Y.; Tse, C.-W.; Yip, Y.-C.; Tanko, J.; Hudlicky, T. *Chem. Rev.* **1989**, *89*, 165. (b) Reissig, H.-U.; Zimmer, R. *Chem. Rev.* **2003**, *103*, 1151.

(8) (a) Cheng, D.; Kreethadumrongdat, T.; Cohen, T. *Org. Lett.* **2001**, *3*, 2121. (b) Lebel, H.; Marcoux, J.-F.; Molinaro, C.; Charette, A. B. *Chem. Rev.* **2003**, *103*, 977. (c) Long, J.; Yuan, Y.; Shi, Y. *J. Am. Chem. Soc.* **2003**, *125*, 13632.

(9) Yang, D.; Gao, Q.; Lee, C.-S.; Cheung, K.-K. *Org. Lett.* **2002**, *4*, 3271.

(10) (a) Ni, A.; France, J. E.; Davies, H. M. L. *J. Org. Chem.* **2006**, *71*, 5594. (b) Xu, Z.-H.; Zhu, S.-N.; Sun, X.-L.; Tang, Y.; Dai, L.-X. *Chem. Commun.* **2007**, 1960. (c) Hashimoto, T.; Naganawa, Y.; Kano, T.; Maruoka, K. *Chem. Commun.* **2007**, 5143. (d) Thompson, J. L.; Davies, H. M. L. *J. Am. Chem. Soc.* **2007**, *129*, 6090.

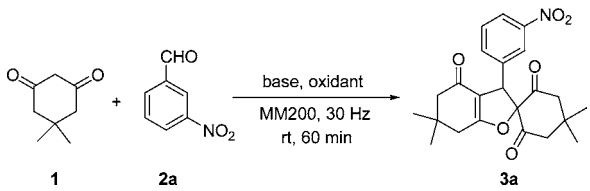
(11) For a review, see: Togo, H.; Iida, S. *Synlett* **2006**, *14*, 2159.

(12) For reviews, see: (a) Wang, G.-W. Fullerene Mechanochemistry. In *Encyclopedia of Nanoscience and Nanotechnology*; Nalwa, H. S. Ed.; American Scientific Publishers: Stevenson Ranch, 2004; Vol. 3, p 557. (b) Komatsu, K. *Top. Curr. Chem.* **2005**, *254*, 185. (c) Rodríguez, B.; Bruckmann, A.; Rantanen, T.; Bolm, C. *Adv. Synth. Catal.* **2007**, *349*, 2213. (d) Garay, A. L.; Pichon, A.; James, S. L. *Chem. Soc. Rev.* **2007**, *36*, 846. (e) Bruckmann, A.; Krebs, A.; Bolm, C. *Green Chem.* **2008**, *10*, 1131. (f) Kaupp, G. *CrystEngComm* **2009**, *11*, 388.

(13) (a) Zhang, Z.; Dong, Y.-W.; Wang, G.-W.; Komatsu, K. *Synlett* **2004**, 61. (b) Zhang, Z.; Wang, G.-W.; Miao, C.-B.; Dong, Y.-W.; Shen, Y.-B. *Chem. Commun.* **2004**, 1832. (c) Zhang, Z.; Gao, J.; Xia, J.-J.; Wang, G.-W. *Org. Biomol. Chem.* **2005**, *3*, 1617. (d) Wang, G.-W.; Wu, X.-L. *Adv. Synth. Catal.* **2007**, *349*, 1977. (e) Wu, X.-L.; Xia, J.-J.; Wang, G.-W. *Org. Biomol. Chem.* **2008**, *6*, 548. (f) Gao, J.; Wang, G.-W. *J. Org. Chem.* **2008**, *73*, 2955.

(14) For selected examples in other groups, see: (a) Balema, V. P.; Wiench, J. W.; Pruski, M.; Pecharsky, V. K. *J. Am. Chem. Soc.* **2002**, *124*, 6244. (b) Rodríguez, B.; Tantanen, T.; Bolm, C. *Angew. Chem., Int. Ed.* **2006**, *45*, 6924. (c) Schneider, F.; Ondruschka, B. *ChemSusChem* **2008**, *1*, 622. (d) Waddell, D. C.; Mack, J. *Green Chem.* **2009**, *11*, 79.

Table 1. Optimization of Additives for the Reaction of Dimedone with 3-Nitrobenzaldehyde under Mechanical Milling Conditions[a]

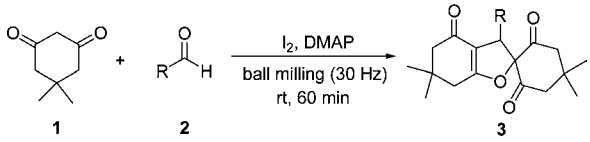


entry	base	promoter	yield (%)
1	DMAP	I_2	91
2	DMAP	CBr_4	54
3	DMAP	NBS	35
4	DMAP	NCS	26
5	DMAP	Oxone/NaBr	21
6	DMAP	Oxone/$ZnCl_2$	
7	Na_2CO_3	I_2	trace
8	Na_2CO_3	I_2	trace
9	Cs_2CO_3	I_2	58
10	K_2CO_3	I_2	67
11	DABCO	I_2	57
12	DBU	I_2	29

[a] Dimedone (2.4 equiv), 3-nitrobenzaldehyde (1.0 equiv), base (2.5 equiv), and promoter (1.65 equiv) in a ball mill.

aldehydes were investigated to react with dimedone, and the results are listed in Table 2. Various aromatic aldehydes with

Table 2. Reaction of Dimedone with Aldehydes Mediated by I_2/DMAP under Mechanical Milling Conditions[a]



entry	R	product	yield (%)
1	3-$NO_2C_6H_4$ (**2a**)	**3a**	91
2	4-$NO_2C_6H_4$ (**2b**)	**3b**	92
3	4-CNC_6H_4 (**2c**)	**3c**	88
4	3,4-$Cl_2C_6H_3$ (**2d**)	**3d**	86
5	4-$CHOC_6H_4$ (**2e**)	**3e**	83
6	4-$CH_3OC_6H_4$ (**2f**)	**3f**	81
7	3,4-$(CH_3)_2C_6H_3$ (**2g**)	**3g**	82
8	3,4-$(OCH_3)_2C_6H_3$ (**2h**)	**3h**	84
9	H (**2i**)	**3i**	79
10	Et (**2j**)	**3j**	86
11	n-Pr (**2k**)	**3k**	85
12	 (**2l**)	**3l**	77
13	 (**2m**)	**3m**	80
14	 (**2n**)	**3n**	85

[a] Dimedone (2.4 equiv), aldehyde (1.0 equiv), DMAP (2.5 equiv), and iodine (1.65 equiv) in a ball mill.

substituents of different electronic property reacted smoothly and efficiently under the present conditions, affording the corresponding dihydrofuran products in good to excellent yields. The aldehyde with an electron-withdrawing group gave a higher yield than that bearing an electron-donating group (entries 1−8, Table 2). Aliphatic aldehydes, including paraformaldehyde, propionic aldehyde, and butyraldehyde, were also investigated. Smooth reactions were observed for these aldehydes and delivered the final products in good yields (entries 9−11, Table 2). To our great delight, heteroaromatic aldehydes, such as 2-pyridinecarboxaldehyde, 2-thiophenecarboxaldehyde, and 2-furancarboxaldehyde, were also tolerated under the current conditions, furnishing the dihydrofuran products in good yields (entries 12−14, Table 2).

To further demonstrate the superiority of our methodology and to extend the utility of this oxidative cycloaddition, another 1,3-dicarbonyl compound, i.e., 1,3-indandione (**4**), was also explored. When 1,3-indandione was treated with 3-nitrobenzaldehyde under similar conditions, a new type of compound was obtained rather than the expected dihydrofuran. On the basis of the spectral analysis, the structure of this new compound was identified to be a bispiro-substituted cyclopropane derivative **5a**, which was further confirmed by single-crystal X-ray diffraction analysis (Figure 2).

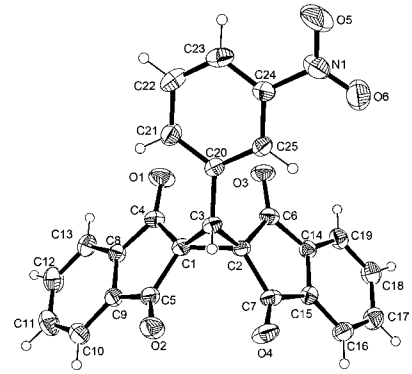
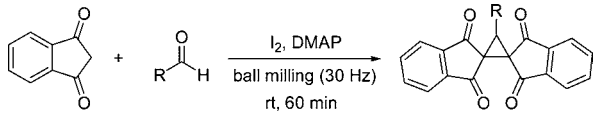


Figure 2. X-ray crystal structure of **5a**.

Then a number of substituted aldehydes were investigated to react with 1,3-indandione to explore the scope and generality of this cyclopropanation reaction. The results are summarized in Table 3. As shown in Table 3, all of the aldehydes bearing electron-withdrawing groups could react with 1,3-indandione and gave the corresponding cyclopropanes **5** as the exclusive products in good yields (entries 1−7, Table 3). When benzaldehyde was employed, the desired product was obtained in a relatively low yield (69%, entry 8, Table 3). Surprisingly, the reactions of electron-rich aromatic aldehydes, aliphatic aldehydes, and heteroaromatic aldehydes were not very successful. That is, the corresponding cyclopropanes were formed in low yields. For example, product **5r** was obtained in only 60% (entry 9, Table 3).

It should be pointed out the reactions shown in Tables 2 and 3 could also proceed in traditional liquid phase. For

Table 3. Reaction of 1,3-Indandione with Aldehydes Mediated by I_2/DMAP under Mechanical Milling Conditions[a]



4 2 5

entry	R	product	yield (%)
1	3-$NO_2C_6H_4$ (**2a**)	**5a**	88
2	4-$NO_2C_6H_4$ (**2b**)	**5b**	89
3	4-CNC_6H_4 (**2c**)	**5c**	84
4	3,4-$Cl_2C_6H_3$ (**2d**)	**5d**	80
5	4-$CHOC_6H_4$ (**2e**)	**5e**	75
6	4-BrC_6H_4 (**2o**)	**5o**	82
7	4-ClC_6H_4 (**2p**)	**5p**	83
8	C_6H_5 (**2q**)	**5q**	69
9	4-$CH_3C_6H_4$ (**2r**)	**5r**	60

[a] 1,3-Indandione (2.7 equiv), aldehyde (1.0 equiv), DMAP (2.5 equiv), and iodine (1.65 equiv) in a ball mill.

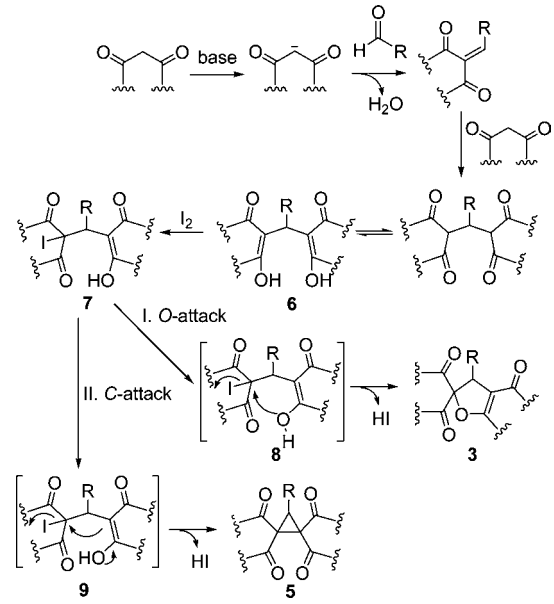
example, the reaction of **1** with **2a** and that of **4** with **2a** in 1,4-dioxane at room temperature for 1 h afforded **3a** and **5a** in 77% and 59% yields, respectively. However, this procedure required the use of an organic solvent, and the yields were lower. It is noteworthy that liquid aldehydes could also be employed in the reactions with both dimedone and 1,3-indandione (see Tables 2 and 3), and the reaction medium in the jar was solid alike because all other three components were excess and solid.

Control experiments showed that only condensation product **6** from two molecules of the 1,3-dicarbonyl compound and one molecule of the aldehyde was obtained if the reaction was performed without molecular iodine. Accordingly, compound **6** seemed to be an intermediate of this reaction. Moreover, when bis-adduct **6** was employed as the starting material instead of the combination of the 1,3-dicarbonyl compound and aldehyde, the desired product was also obtained in similar yield.

Although the exact mechanism of this transformation is not clear right now, a possible reaction mechanism is proposed (Scheme 1) based on the above results and the known literature. It was reported that the reaction of a 1,3-dicarbonyl compound with iodine gave the α-iodonated product.[9,15] Similarly, the reaction of compound **6** with iodine gave iodide **7** as the key intermediate. And then there were

(15) (a) Nierengarten, J.-F.; Gramlich, V.; Cardullo, F.; Diederich, F. *Angew. Chem., Int. Ed.* **1996**, *35*, 2101. (b) Gogoi, S.; Bhuyan, R.; Barua, N. C. *Synth. Commun.* **2005**, *35*, 2811. (c) Tsukano, C.; Siegel, D. R.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2007**, *46*, 8840.

Scheme 1. Proposed Mechanism of the Formation of Spiro Dihydrofurans and Cyclopropanes



two pathways to proceed. An intramolecular nucleophilic *O*-attack via **8** (path I) with an elimination of HI afforded dihydrofurans **3**. Alternatively, the nucleophilic *C*-attack via **9** (path II) with an elimination of HI gave cyclopropanes **5**.[9]

In summary, we have presented a versatile one-pot and solvent-free reaction of dimedone and 1,3-indandione with aldehydes to selectively afford spiro dihydrofurans and cyclopropanes in good yields under mechanical milling conditions. These iodine-mediated oxidative cycloadditions provide a rapid and efficient route to the preparation of a variety of spiro dihydrofuran and cyclopropane derivatives.

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Supporting Information Available: Detailed descriptions of experimental procedures and characterization of compounds; ^1H NMR and ^{13}C NMR spectra of **3a**−**n**, **5a**−**e**, and **5o**−**r**; crystal structure data (CIF) of **3a** and **5a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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