# Cyclization of malonate derivatives with iodine(III) reagents

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Abstract: The cyclization of malonate derivatives using hypervalent iodine(III) reagents is described. In this reaction, double bonds are dioxygenated and 5-membered lactones obtained with up to 70% yield and in diastereomeric ratios of up to 11:1.

Hypervalent iodine reagents have become extremely versatile reagents in organic chemistry. The mild reaction conditions associated with the low toxicity and the environmentally friendly behavior of these compounds render them attractive to use in organic synthesis.[1] Hypervalent iodine reagents are very selective oxidants[2] and several derivatives have been reported as enantiomerically pure reagents.[3] Due to their electrophilic nature and their excellent leaving group ability, they can react with a broad range of nucleophiles in reactions such as the oxidation of sulfides to sulfoxides,[4] the dearomatization of phenols,[5] the α-arylation[6] and the α-oxygenation of carbonyl compounds[7] but also in the functionalization of carbon-carbon double bonds through dioxygenation[8], diamination[9], oxyamination,[10] iodoamination,[11] oxytrifluoromethylation[12] or aminofluorination.[13] The facile generation of cationic intermediates by hypervalent iodine reagents allows either the direct reaction with a nucleophile or the formation of rearranged products[14] with ring contraction,[15] ring expansion,[16] or aryl migration.[17] Finally, intensive efforts have been made towards the catalytic use of those hypervalent iodine reagents.[3b,18]

Herein we report the intramolecular synthesis of lactones from malonate derivatives using hypervalent iodine reagents. Initially, investigations were carried out using substrate **1** which was easily synthesized from dimethyl malonate by two subsequent alkylations. The reaction was initially performed using only the iodine(III) reagent at –20 °C. Both PhI(OAc)$_2$ and I(OAc)$_3$ did not mediate any cyclization even after 3 days of reaction and the starting material was fully recovered (Table 1, Entries 1 and 2). It was suspected that the iodine reagent alone was not reactive enough and an activating Lewis acid was added. With the Lewis acid BF$_3$•OEt$_2$ the cyclized product **2a** was isolated in 16% yield and with a 10:1 diastereomeric ratio (Table 1, Entry 3). The size of the lactone ring was unambiguously established from its crystal structure (Figure 1).[19] The crystal structure also revealed the relative stereochemistry of the major diastereomer, with the methyl ester and the CH$_2$-acetate substituent being *trans* to each other.
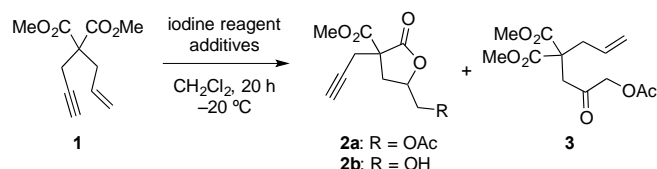
Table 1. Optimization of reaction conditions for lactonization.

Entry	Iodine reagent (Eq.)	Additive (Eq.)	Yield [%]	d.r. (*trans*:*cis*)
1	PhI(OAc)$_2$ (1)	-	0	-
2	I(OAc)$_3$ (1)	-	0	-
3	PhI(OAc)$_2$ (1)	BF$_3$ • OEt$_2$ (2)	**2a**: 16	10:1
4[a]	PhI(OAc)$_2$ (1.2)	BF$_3$ • OEt$_2$ (2)	**2a**: 15	10:1
5[b]	PhI(OAc)$_2$ (1.2)	BF$_3$ • OEt$_2$ (2)	**2a**: 48 **3**: 45	6:1
6	PhI(OH)OTs (1.2)	BF$_3$ • OEt$_2$ (2)	**2b**: 20	n.d.[c]
7	PhI(OCOCF$_3$)$_2$ (1.5)	BF$_3$ • OEt$_2$ (2)	0	-
8	PhI(OAc)$_2$ (1.2)	BF$_3$ • OEt$_2$ (3)	**2a**: (83)[d]	5:1
9	PhI(OAc)$_2$ (1.2)	BF$_3$ • OEt$_2$ (2) AcOH (12.5)	**2a**: 24 **3**: 32	8:1
10	PhI(OAc)$_2$ (1.2)	BF$_3$ • OEt$_2$ (3) AcOH (12.5)	**2a**: 58 **3**: 6	11:1
11	PhI(OAc)$_2$ (1.2)	BF$_3$ • OEt$_2$ (2) H$_2$O (0.01)	**2a**: 39	5:1

[a] Reaction time: 3 days. [b] Reaction performed at 0 ºC. A reaction performed at rt led to almost complete decomposition. [c] Not determined. [d] Conversion, yield not determined.
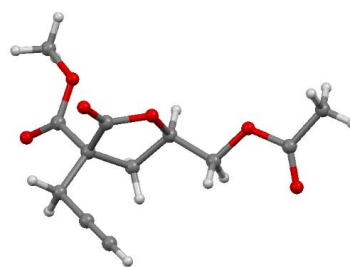
Figure 1. Crystal structure of lactone **2a**.

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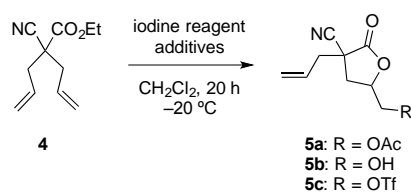   Homepage: http://blogs.cardiff.ac.uk/wirth/

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A slight excess of the iodine reagent did not make any difference and the diastereomeric ratio remained unchanged (Table 1, Entry 4). The yield was not improved by prolonging the reaction time to three days. Increasing the temperature to 0 °C improved the conversion to 100% and the cyclized product **2a** was isolated in 48% yield. However, the formation of a major side product was observed. A competing oxidation of the triple bond occurred and the oxidized compound **3** was isolated in 45% yield in addition to **2** (Table 1, Entry 5). When the reaction was warmed up to room temperature, considerable decomposition was observed and products could no longer be isolated.

Two other iodine reagents were also evaluated. Koser's reagent [PhI(OH)OTs] gave the cyclized product **2b** (R = OH) in only 20% yield. The selectivity could not be determined by ^{1}H NMR as the peaks were overlapping (Table 1, Entry 6). Using [bis(trifluoroacetoxyiodo)]benzene together with BF$_3$ • OEt$_2$ led to complete decomposition (Table 1, Entry 7).

Increasing the amount of BF$_3$ • OEt$_2$ to 3 equivalents led to a better conversion (83%), but the selectivity dropped to a diastereomeric ratio of 5:1 (Table 1, Entry 8). Additional acetic acid was added to the reaction mixture and the cyclized product was isolated in 58% yield with slightly improved diastereomeric ratio of 11:1 (Table 1, Entry 10). As the increased amount of Lewis acid was detrimental for the selectivity, the reaction was also performed with only two equivalents of BF$_3$ • OEt$_2$. The starting material was fully converted but surprisingly, more side product **3** was formed as well as one other uncharacterized side product. Furthermore, the selectivity decreased to a ratio of 8:1 (Table 1, Entry 9). Finally, it has to be noted than in the presence of 1 mol% water the cyclization still proceeded but with a lower conversion. Only product **2b** was isolated in 39% yield and with a diastereomeric ratio of 5:1 (Table 1, Entry 11).

The influence of the solvent was also studied. When the reaction was performed in acetonitrile, no product was isolated due to complete degradation of the reaction mixture into uncharacterized products. The addition of acetic acid did not lead to a cleaner reaction. 2,2,2-Trifluoroethanol (TFE) is known to coordinate to the iodine reagents and has, in several cases of iodine(III)-mediated reactions, led to increased selectivities.[20] However, when a mixture of dichloromethane and TFE (5:1) was used as the solvent, complete degradation of the starting material was observed.

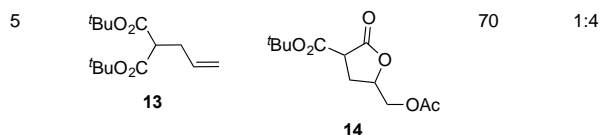| 3 | PhI(OAc)$_2$ (1.2) | TMSOTf (2) TFE | 0 | - |
4	PhIO (1)	BF$_3$ • OEt$_2$ (2)	**5b**: 37	n.d.[c]
5	PhI(OH)OTs (1.5)	BF$_3$ • OEt$_2$ (2)	**5b**: 21	2:1
6	PhI(OCOCF$_3$)$_2$ (1.5)	BF$_3$ • OEt$_2$ (2)	0	-

[a] Reaction time: 3 days. [b] Reaction performed at 0 °C. A reaction performed at rt led to almost complete decomposition. [c] Not determined.

The cyclization reaction was also performed with ethyl 2-cyanoacetate derivative **4**, which was easily prepared from ethyl 2-cyanoacetate. The expected cyclized product **5a** with the acetoxy group addition was isolated in 43% yield but the diastereomeric ratio was only 3:1 (Table 2, Entry 1). Another Lewis acid (TMSOTf) was also used here. The cyclization occurred with lower yield (28%) while the triflate anion reacted as the nucleophile to give product **5c** (Table 2, Entry 2). The addition of TFE resulted again in complete degradation of the starting material (Table 2, Entry 3). Changing the iodine(III) reagent did neither improve the yield of the cyclized product **5** nor the selectivity. Iodosylbenzene and Koser's reagent both mediated the addition of a hydroxyl group onto the double bond in 37% and 21% yield, respectively (Table 2, Entries 4 and 5). Finally, the use of [bis(trifluoroacetoxyiodo)]benzene resulted in complete degradation into unknown products (Table 2, Entry 6).

After the detailed investigation of the two substrates **1** and **4**, different homoallyl esters were cyclized under identical conditions. The results are summarized in Table 3.

Table 2. Cyclization of ethyl 2-cyanoacetate derivative **4**.

Entry	Iodine reagent (Eq.)	Additive (Eq.)	Yield [%]	d.r. (*trans*:*cis*)
1	PhI(OAc)$_2$ (1.2)	BF$_3$ • OEt$_2$ (2)	**5a**: 43	3:1
2	PhI(OAc)$_2$ (1.2)	TMSOTf (2)	**5c**: 28	n.d.[c]

Table 3. Cyclization of homoallyl esters.[a]

Entry	Substrate	Product	Yield [%]	d.r. (*trans*:*cis*)
1	**6**	**7**	61	1:1.3
2[b]	**8**	**9**	15	n.d.[c]
3	**10**	**2a**: R = OAc **2b**: R = OH	**2a**: 28 **2b**: 13	n.d.[c] n.d.[c]
4	**11**	**12**	58	1:4

| 5 | | 70 | 1:4 |

The mono-allylated dimethyl malonate **6** gave compound **7** in 61% yield and with a diastereomeric ratio of 1.3:1 (Table 3, Entry 1). The cyclization also proceeded with the di-allylated substrate **8**. As two carbon-carbon double bonds and two esters are present in compound **8** the amounts of reagents were increased and the double cyclized spiro product **9** was isolated in 15% yield as the major product (Table 3, Entry 2). Even if the substrate contains one hydrolyzed ester group as in **10** there seems to be no apparent advantage for the cyclization. Two different cyclized products were formed during the reaction, one with the addition of a hydroxyl group onto the double bond (**2b**, 13%) and the other one with an acetoxy moiety (**2a**, 28% yield) (Table 3, Entry 3).

Di-*tert*-butyl malonate derivatives can be used similarly well. Substrate **11** gave the desired cyclized product **12** in reasonable yield (58%) and with moderate selectivity (d.r. = 4:1) (Table 3, Entry 4). The mono-allylated di-*tert*-butyl malonate **13** led to the cyclized product **14** in good yield (70%) but with only moderate selectivity of 4:1 (Table 3, Entry 5). The stereochemistry of the major isomer (*cis*) was determined by a NOESY experiment (see supporting information).

The substitution of (diacetoxyiodo)benzene with a chiral derivative[21] did not lead to any cyclization product, probably due to reduced reactivity of the chiral reagent.

In conclusion, several malonate derivatives were successfully cyclized to highly functionalized lactones with moderate to good diastereoselectivities.

Experimental Section

PhI(OAc)₂ (108 mg, 0.340 mmol) was dissolved in dry dichloromethane (2 mL) under argon and the reaction was cooled down to –20 °C. BF₃ • OEt₂ (70 μL, 0.56 mmol) and AcOH (200 μL, 3.5 mmol) was then added and the resulting mixture was stirred for 5 min. A solution of starting material (0.28 mmol) in dry dichloromethane (2 mL) was then added and the resulting mixture was stirred for 19 h at –20 °C. The reaction was quenched with sat. aq. solution of sodium bicarbonate (0.5 mL) and the organic phase was extracted with dichloromethane (3 x 5 mL). The combined organic layers were dried through a Telos® phase separator and concentrated under vacuum. The pure product was obtained after purification by column chromatography (0 to 30% EtOAc in hexane).

Acknowledgements

[1] a) *Hypervalent Iodine Chemistry*, Ed. T. Wirth, *(Topics in Current Chemistry)*, Springer, Berlin, **2016**, vol. 373. b) V. V. Zhdankin, *Hypervalent Iodine Chemistry*, Wiley, Chichester, **2014**.

[2] T. Wirth, *Angew. Chem. Int. Ed.* **2005**, *44*, 3656-3665.

[3] a) R. Kumar, T. Wirth, *Top. Curr. Chem.* **2016**, *373*, 243-261; b) F. Berthiol, *Synthesis* **2015**, *47*, 587-603; c) F. V. Singh, T. Wirth, *Chem. Asian J.* **2014**, *9*, 950-972; d) A. Parra, S. Reboredo, *Chem. Eur. J.* **2013**, *19*, 17244-17260; e) U. Farid, T. Wirth, in *Asymmetric Synthesis – The Essentials*, Eds.: S. Bräse, C. Christmann, Wiley VCH, **2012**, 197-203; f) H. Liang, M. A. Ciufolini, *Angew. Chem. Int. Ed.* **2011**, *50*, 11849-11851; g) M. Ngatimin, D. W. Lupton, *Aust. J. Chem.* **2010**, *63*, 653-658.

[4] a) S. M. Altermann, S. Schäfer, T. Wirth, *Tetrahedron* **2010**, *66*, 5902-5907; b) V. V. Zhdankin, J. T. Smart, P. Zhao, P. Kiprof, *Tetrahedron Lett.* **2000**, *41*, 5299-5302; c) H. Tohma, S. Takizawa, H. Watanabe, Y. Fukuoka, T. Maegawa, Y. Kita, *J. Org. Chem.* **1999**, *64*, 3519-3523; d) D. G. Ray, G. F. Koser, *J. Am. Chem. Soc.* **1990**, *112*, 5672-5673; e) T. Imamoto, H. Koto, *Chem. Lett.* **1986**, 967-968.

[5] a) A. M. Harned, *Tetrahedron Lett.* **2014**, *55*, 4681-4689; b) K. A. Volp, A. M. Harned, *Chem. Commun.* **2013**, *49*, 3001-3003; c) M. Uyanik, T. Yasui, K. Ishihara, *Angew. Chem. Int. Ed.* **2013**, *52*, 9215-9218; d) T. Dohi, N. Takenaga, T. Nakae, Y. Toyoda, M. Yamasaki, M. Shiro, H. Fujioka, A. Maruyama, Y. Kita, *J. Am. Chem. Soc.* **2013**, *135*, 4558-4566; e) S. Quideau, G. Lyvinec, M. Marguerit, K. Bathany, A. Ozanne-Beaudenon, T. Buffeteau, D. Cavagnat, A. Chénedé, *Angew. Chem. Int. Ed.* **2009**, *48*, 4605-4609.

[6] a) M. Brown, M. Delorme, F. Malmedy, J. Malmgren, B. Olofsson, T. Wirth, *Synlett* **2015**, *26*, 1573-1577; b) V. K. Aggarwal, B. Olofsson,

Angew. Chem. Int. Ed. **2005**, *44*, 5516-5519; c) M. Ochiai, Y. Kitagawa, N. Takayama, Y. Takaoka, M. Shiro, *J. Am. Chem. Soc.* **1999**, *121*, 9233-9234.

[7] a) B. Basdevant, C. Y. Legault, *J. Org. Chem.* **2015**, *80*, 6897-6902; b) B. Basdevant, C. Y. Legault, *Org. Lett.* **2015**, *17*, 4918-4921; c) P. Mizar, T. Wirth, *Angew. Chem. Int. Ed.* **2014**, *53*, 5993-5997; d) U. Farooq, S. Schäfer, A.-H. Shah, D. Freudendahl, T. Wirth, *Synthesis* **2010**, *2010*, 1023-1029; e) S. M. Altermann, R. D. Richardson, T. K. Page, R. K. Schmidt, E. Holland, U. Mohammed, S. M. Paradine, A. N. French, C. Richter, A. M. Bahar, B. Witulski, T. Wirth, *Eur. J. Org. Chem.* **2008**, 5315-5328; f) R. Richardson, T. Page, S. Altermann, S. Paradine, A. French, T. Wirth, *Synlett* **2007**, 538-542; E. Hatzigrigoriou, A. Varvoglis, M. Bakola-Christianopoulou, *J. Org. Chem.* **1990**, *55*, 315-318.

[8] a) T. Takesue, M. Fujita, T. Sugimura, H. Akutsu, *Org. Lett.* **2014**, *16*, 4634-4637; b) M. Shimogaki, M. Fujita, T. Sugimura, *Eur. J. Org. Chem.* **2013**, 7128-7138; c) M. Fujita, K. Mori, M. Shimogaki, T. Sugimura, *Org. Lett.* **2012**, *14*, 1294-1297; d) M. Fujita, Y. Yoshida, K. Miyata, A. Wakisaka, T. Sugimura, *Angew. Chem. Int. Ed.* **2010**, *49*, 7068-7071; e) M. Fujita, Y. Ookubo, T. Sugimura, *Tetrahedron Lett.* **2009**, *50*, 1298-1300; f) M. Fujita, S. Okuno, H. J. Lee, T. Sugimura, T. Okuyama, *Tetrahedron Lett.* **2007**, *48*, 8691-8694; g) U. H. Hirt, M. F. H. Schuster, A. N. French, O. G. Wiest, T. Wirth, *Eur. J. Org. Chem.* **2001**, 1569-1579; h) T. Wirth, U. H. Hirt, *Tetrahedron: Asymmetry* **1997**, *8*, 23-26.

[9] a) P. Mizar, A. Laverny, M. El-Sherbini, U. Farid, M. Brown, F. Malmedy, T. Wirth, *Chem. Eur. J.* **2014**, *20*, 9910-9913; b) C. Röben, J. A. Souto, E. C. Escudero-Adán, K. Muñiz, *Org. Lett.* **2013**, *15*, 1008-1011; c) C. Röben, J. A. Souto, Y. González, A. Lishchynskyi, K. Muñiz, *Angew. Chem. Int. Ed.* **2011**, *50*, 9478-9482.

[10]   U. Farid, T. Wirth, *Angew. Chem. Int. Ed.* **2012**, *51*, 3462-3465.

[11]   a) P. Mizar, T. Wirth, *Synthesis* **2016**, *48*, in press; b) P. Mizar, A. Burrelli, E. Günther, M. Söftje, U. Farooq, T. Wirth, *Chem. Eur. J.* **2014**, *20*, 13113-13116.

[12]   R. Zhu, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2013**, *52*, 12655-12658.

[13]   a) H. Chen, A. Kaga, S. Chiba, *Org. Biomol. Chem.* **2016**, *16*, 5481-5485; b) W. Kong, P. Feige, T. de Haro, C. Nevado, *Angew. Chem. Int. Ed.* **2013**, *52*, 2469-2473.

[14]   a) G. Maertens, S. Canesi, *Top. Curr. Chem.* **2016**, *373*, 223-242; b) F. V. Singh, T. Wirth, *Synthesis* **2013**, *45*, 2499-2511; c) G. Jacquemot, S. Canesi, *J. Org. Chem.* **2012**, *77*, 7588-7594; d) F. V Singh, J. Rehbein, T. Wirth, *ChemistryOpen* **2012**, *1*, 245-250; e) M.-A. Beaulieu, C. Sabot, N. Achache, K. C. Guérard, S. Canesi, *Chem. Eur. J.* **2010**, *16*, 11224-11228; f) A. A. Zagulyaeva, C. T. Banek, M. S. Yusubov, V. V Zhdankin, *Org. Lett.* **2010**, *12*, 4644-4647; g) J.-M. Vatèle, *Synlett* **2008**, 1785-1788.

[15]   a) L. F. Silva, F. A. Siqueira, E. C. Pedrozo, F. Y. M. Vieira, A. C. Doriguetto, *Org. Lett.* **2007**, *9*, 1433-1436; b) L. F. Silva, *Molecules* **2006**, *11*, 421-434; c) F. A. Siqueira, E. E. Ishikawa, A. Fogaça, A. T. Faccio, V. M. T. Carneiro, R. R. S. Soares, A. Utaka, I. R. M. Tébéka, M. Bielawski, B. Olofsson, L. F. Silva, *J. Braz. Chem. Soc.* **2011**, *22*, 1795-1807.

[16]   a) L. F. Silva, R. S. Vasconcelos, M. A. Nogueira, *Org. Lett.* **2008**, *10*, 1017-1020; b) M. Justik, G. Koser, *Molecules* **2005**, *10*, 217-225.

[17]   a) M. Brown, R. Kumar, J. Rehbein, T. Wirth, *Chem. Eur. J.* **2016**, *22*, 4030-4035; b) S. M. Banik, J. W. Medley, E. N. Jacobsen, *Science* **2016**, *353*, 51-54; c) U. Farid, F. Malmedy, R. Claveau, L. Albers, T. Wirth, *Angew. Chem. Int. Ed.* **2013**, *52*, 7018-7022; d) A. C. Boye, D. Meyer, C. K. Ingison, A. N. French, T. Wirth, *Org. Lett.* **2003**, *5*, 2157-2159.

[18]   R. D. Richardson, T. Wirth, *Angew. Chem. Int. Ed.* **2006**, *45*, 4402-4404.

[19]   CCDC-1512668 (**2a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[20]   T. Dohi, N. Yamaoka, Y. Kita, *Tetrahedron* **2010**, *66*, 5775–5785.

[21]   The chiral reagent dimethyl-2,2'-((2-(diacetoxy-λ^3-iodanyl)-1,3-phenylene)bis(oxy))(2*R*,2'*R*)-dipropionate was investigated in this reaction, see : M. Uyanik, T. Yasui, K. Ishihara, *Angew. Chem. Int. Ed.* **2010**, *49*, 2175-2177.