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Synthesis of phthalides utilizing a one-pot intramolecular domino protocol†

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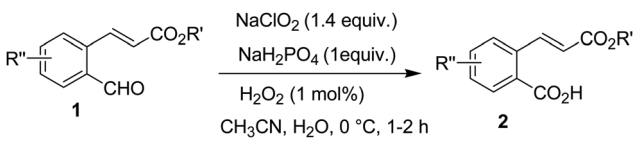
A number of (*E*)-3-alkylidine-phthalide derivatives have been prepared at room temperature in excellent yields in a one-pot reaction by treating *o*-alkenylbenzoic acids with *meta*-chloroperbenzoic acid and *para*-toluenesulfonic acid. This reaction presumably occurs *via* domino epoxidation – intramolecular cyclization – acid catalyzed dehydration sequence of reactions. On the other hand, 3-(2-formyl-3,4-dihydro-naphthalen-1-yl)-acrylic acid esters and 3-(2-formyl-3,4-dihydro-naphthalen-1-yl)-acrylonitriles afforded phthalide derivatives under Pinnick reaction conditions involving oxidation-intramolecular Michael addition.

1(3*H*)-Isobenzofuranones or phthalides, fused-ring aromatic γ-lactones, have attracted the attention of various research groups, regarding their isolation, structural elucidation, biogenesis, biological activity as well as synthetic goals. In particular, the importance of 3-substituted phthalide frameworks is underscored by their wide distribution in a large collection of natural products with broad and potentially path-pointing biological activities.[1]

Phthalides are of special interests in polymer science in view of their ring-chain isomerism. Phthalide-containing polymers possess outstanding electrophysical and optical characteristics and high heat resistance.[2]

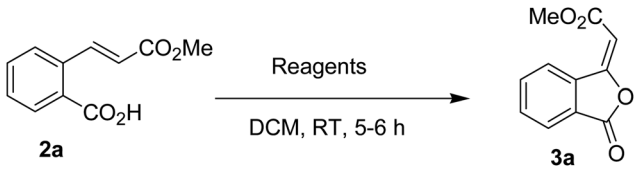
Since the classical work by Bistrzycki *et al.*,[3] numerous methods have been reported for the synthesis of phthalides. Amongst them, the use of *o*-halobenzoic acid derivatives and terminal alkynes as starting materials is one of the most attractive routes.[4] The first one pot synthesis of phthalides was described by Castro *et al.*, but the methodology afforded mixture of phthalides and isocoumarins.[5] Of late, Phan *et al.* demonstrated an intramolecular hydroacylation reaction of ketones catalyzed by rhodium for the synthesis of phthalides.[6] In continuation of our synthetic efforts for the development of newer methods for the preparation of heterocycles,[7] we herein present an efficient, one-pot room temperature route to phthalide and 3-alkylidine-phthalide derivatives *via* intramolecular domino protocol.

Current assignment started with the conversion of *o*-alkenylbenzaldehydes[8] **1** into *o*-alkenylbenzoic acids **2** exploiting Pinnick oxidation[9] (Scheme 1). When the precursors **1** were treated with sodium chlorite (1.4 equiv.) in the presence of



Scheme 1 Synthesis of *o*-alkenylbenzoic acids by Pinnick oxidation.

Table 1 Optimization study of cyclization *o*-alkenylbenzoic acids[a]



Entry	*m*CPBA	*p*-TsOH	Yield[b] (%)
1	—	1.0 mmol	NR
2	1.0 mmol	—	Dec
3	1.0 mmol	1.0 mmol	93

[a] *Reaction conditions*: reaction was carried out with 2-(2-methoxycarbonyl-vinyl)-benzoic acid **2a** (1.0 mmol), *m*CPBA(1.0 mmol) and *p*-TsOH (1.0 mmol) in DCM (5 mL) at room temperature for 5–6 h. [b] Isolated yields after purification by column chromatography. NR: no other reaction and complete recovery of the starting material. Dec: decomposition of the starting material.

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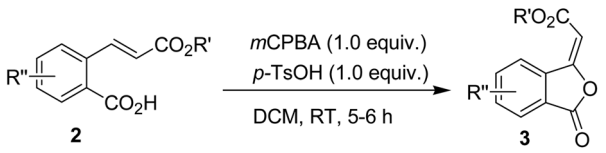
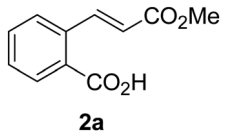
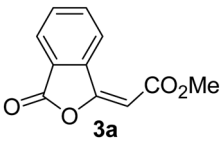
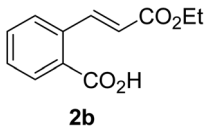
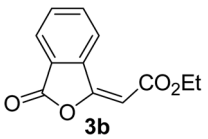
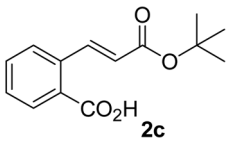
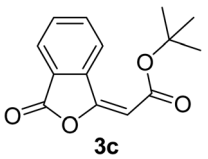
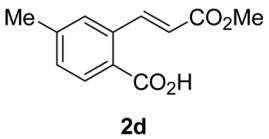
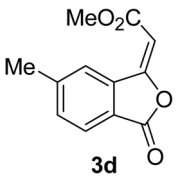
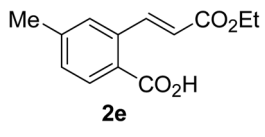
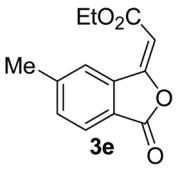
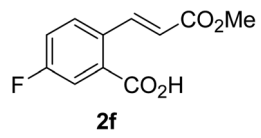
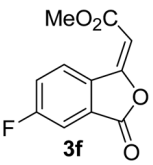
† Electronic supplementary information (ESI) available. See DOI: 10.1039/c3ra45117h

Table 2 Synthesis of 3-alkylidene-phthalides[a]



Entry	Acid **2**	Alkylidine-phthalide **3**	Time (h)	Yield (%)
1	 **2a**	 **3a**	5	93
2	 **2b**	 **3b**	5.5	90
3	 **2c**	 **3c**	6	85
4	 **2d**	 **3d**	5	89
5	 **2e**	 **3e**	6	85
6	 **2f**	 **3f**	6	90

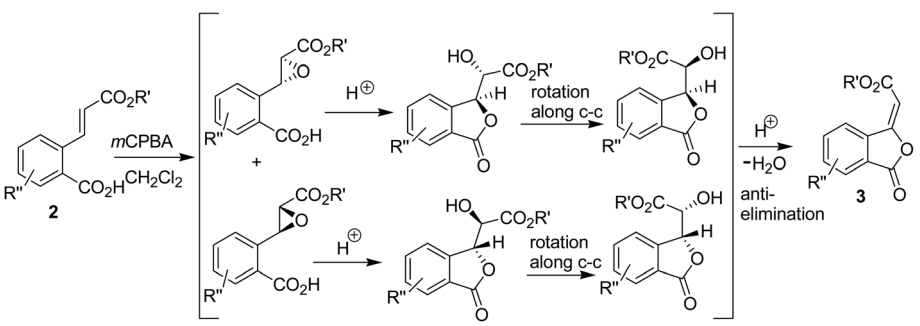
[a] *Reaction condition*: substrate (1.0 mmol), *m*CPBA (1.0 mmol), *p*-TsOH (1.0 mmol), DCM (5 mL), room temperature, 5–6 h.

sodium dihydrogen phosphate buffer (1.0 equiv.) and hydrogen peroxide (1 mol%) in aqueous acetonitrile solvent at 0 °C for 1–2 h, *o*-alkenylbenzoic acids **2** were obtained almost quantitatively.

Our next study was focused on cyclizing model substrate 2-(2-methoxycarbonyl-vinyl)-benzoic acid **2a** into lactone **3a**. A preliminary experiment with **2a** using 1.0 equiv. of *m*CPBA and 1.0 equiv. of *p*-TsOH in dichloromethane at room temperature afforded (*E*)-alkylidine-phthalide **3a** exclusively in 93% yield. Comparing literature report,[10] the *E*-stereochemistry of **3a** was established. The reaction proceeded smoothly, and no trace amount of either isocoumarin or (*Z*)-alkylidine-phthalide was obtained as byproduct. In the absence of *m*CPBA, **2a** was recovered (Table 1, entry 1), while decomposed reaction mixture was obtained in the absence of *p*-TsOH (Table 1, entry 2).

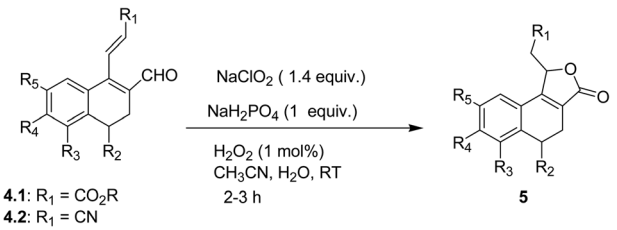
With the optimal conditions in hand, we next probed the generality and scope of the present cyclization reaction with a series of other *o*-alkenylbenzoic acids **2** by varying substituent on benzene ring and ester carbonyl group (Table 2).[11] The strategy not only offered excellent yields of the corresponding (*E*)-alkylidine-phthalides, but also showed tolerance towards sterically demanding tertiary butyl ester (Table 2, entry 3).

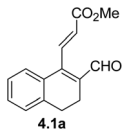
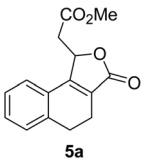
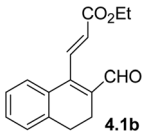
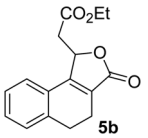
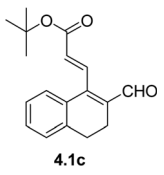
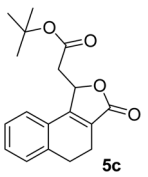
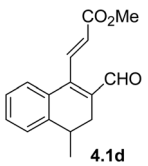
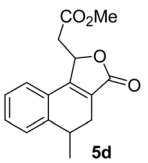
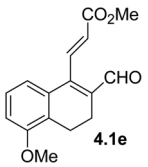
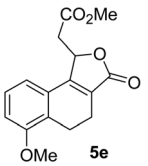
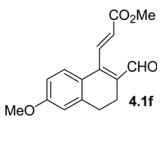
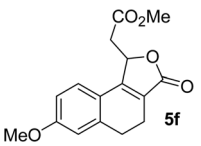
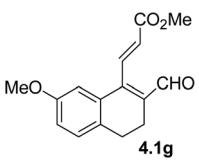
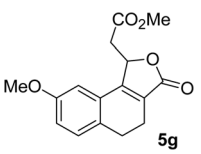
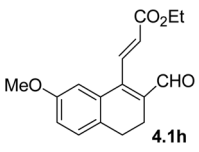
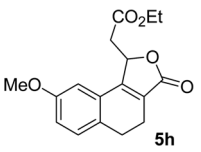
The intramolecular domino cyclization reaction was presumably triggered by the generation of an epoxide (Scheme 2). Our assumption is based on the literature reports[12] where electron-deficient alkene produced epoxides employing *m*CPBA. Then intramolecular anti-attack of the carboxylic acid at the epoxide, followed by acid catalyzed dehydration leads to the alkylidine-phthalide. Absence of the *Z*-product rules out the possibility of E1-mechanism for the dehydration stage. Here elimination of water molecule cannot follow the normal carbocationic pathway, because the electron withdrawing ester group opposes formation of carbocation. This phenomenon resembles acid-catalyzed dehydration of some primary alcohols which does not follow E1-pathway, instead involves E2-elimination as the primary carbocation is highly unfavorable.[13] Similarly, in this case acid-catalyzed E2-elimination of H_2O proceeds. Stereospecificity of the reaction in favor of the *E*-isomer supports E2-mechanism. Even if the initial epoxidation step may be sluggish, subsequent rapid intramolecular attack and dehydration, both of which are entropically favored, accounts for the overall fast reaction rate thereby decreasing reaction time. Also thermodynamic stability of the conjugated alkylidine-phthalides adds to the driving force.



Scheme 2 Plausible mechanism of (*E*)-3-alkylidine phthalide synthesis.

Table 3 Synthesis of lactones



Entry	Formyl-alkene **4**	Lactone **5**	Time (h)	Yield[a] (%)
1			2	99
2			2.5	95
3			3	92
4			2	98
5			2	95
6			2	94
7			2.5	92
8			3	90

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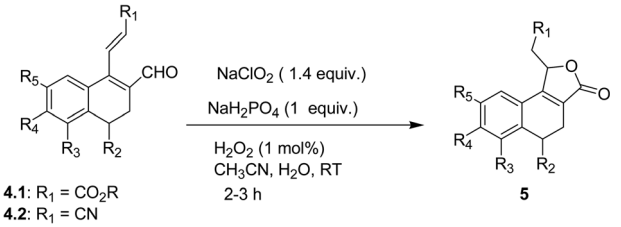
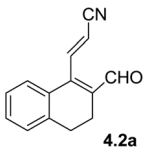
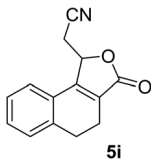
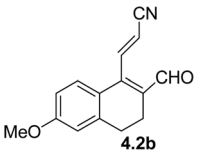
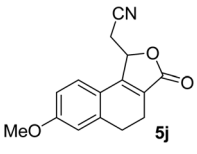
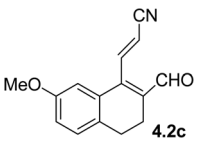
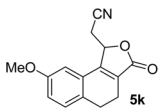


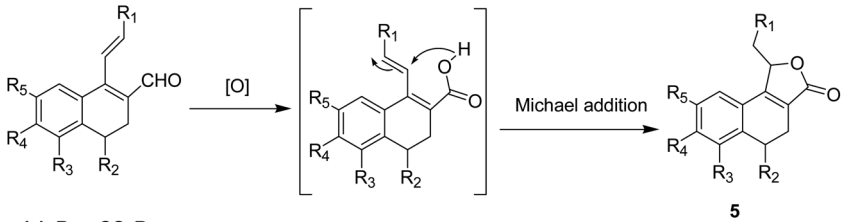
Entry	Formyl-alkene **4**	Lactone **5**	Time (h)	Yield[a] (%)
9			2	95
10			2.5	92
11			3	90

[a] *Reaction conditions*: substrate **4** (1.0 mmol), $NaClO_2$ (1.4 mmol), NaH_2PO_4 (1.0 mmol), H_2O_2 (1 mol%), CH_3CN (2 mL), H_2O (1 mL). Reaction time: 2–3 h. Reaction temp.: RT.

We did not screen alkaline hydrogen peroxide, which is the general reagent for epoxidation of electron deficient-alkene, to avoid additional step to carry out dehydration of the intermediate separately to afford our desired alkylidine-phthalide. Current methodology being one-pot and effective was obviously our primary choice.

To further explore the substrate scope, we then considered replacement of the benzene ring of substrates **2** by dihydronapthalene ring and in order to prepare the corresponding acids when we carried out Pinnick oxidation of 3-(2-formyl-3,4-dihydro-naphthalen-1-yl)-acrylic acid esters[8] **4.1** and 3-(2-formyl-3,4-dihydro-naphthalen-1-yl)-acrylonitriles[8b] **4.2**, to our surprise, lactones **5** were obtained almost quantitatively (Table 3).[14] Here also the lactonization reaction followed domino process. The intermediate acids underwent intramolecular Michael addition reaction in the reaction medium (Scheme 3). Somewhat similar observations were published by Li *et al.* recently, where *o*-alkynylbenzaldehydes afforded phthalides *via* an intramolecular 5-exo-dig cyclization under $NaClO_2$ oxidation conditions.[15]

In conclusion, we have accomplished novel one-pot domino synthetic routes for the construction of phthalides and *E*-alkylidine-phthalides *via* intramolecular lactonization protocol without using any metal catalyst or ligand. While *o*-alkenylbenzoic acids



Scheme 3 Mechanism of lactone synthesis.

provided (*E*)-3-alkylidine-phthalide derivatives under domino epoxidation–heteroannulation–dehydration strategy, formyl-dihydronapthyl substrate offered phthalides simply under $NaClO_2$ oxidation condition. Since the reagent system in either case is cheap and easy to handle, these one-pot methodologies should find practical usage in the synthesis of phthalides, an important class of molecules.

Acknowledgements

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Notes and References

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11 General Procedure for the synthesis of 3-alkylidine phthalides (**3a–f**): to a solution of *o*-alkenylbenzoic acid (1 mmol) in dry DCM (5 mL), *m*CPBA (1 mmol) and *p*-TsOH (1 mmol) was added and the mixture was stirred at rt for 5–6 h. Then the reaction mixture was quenched with saturated aq. $NaHCO_3$ solution and extracted with DCM. The organic solvent was washed with aq $NaHCO_3$ and brine solution, and then dried over Na_2SO_4. The solvent was evaporated and then the product was purified by column chromatography using ethyl acetate/petroleum ether as eluent. Spectral data of representative compounds: (6-Methyl-3-oxo-3*H*-isobenzofuran-1-ylidene)-acetic acid methyl ester (**3d**): white solid. M. P. 122–124 °C. FTIR (KBr, cm^{-1}): 2960, 2362, 1805, 1719, 1650, 1478, 1437, 1210, 1149, 1030, 972, 851, 773, 691. ^1H NMR ($CDCl_3$, 200 MHz): $\delta = 2.54$ (s, 3H), 3.80 (s, 3H), 6.08 (s, 1H), 7.47 (d, $J = 7.8$ Hz, 1H), 7.80 (d, J = 7.8 Hz, 1H), 8.81 (s, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz): $\delta = 22.41$, 51.90, 101.56, 124.05, 125.17, 128.35, 133.63, 136.44, 146.81, 158.23, 165.63, 166.11. HRMS calcd for $C_{12}H_{11}O_4$ (MH^+) $m/z = 219.0657$, found $m/z = 219.0661$. Elemental anal. calcd for $C_{12}H_{10}O_4$: C, 66.05; H, 4.62. Found C, 66.13; H, 4.87%.

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14 General procedure for the synthesis of lactones (**5**): to a solution of 3-(2-formyl-cycloalkenyl)-acrylic esters **4.1** or 3-(2-formyl cycloalkenyl)-acrylonitriles **4.2** (1 mmol) in acetonitrile at 0 °C, NaH_2PO_4 (1 mmol) dissolved in 1 mL

water was added. To it H_2O_2 (1 mol%) was added. Then $NaClO_2$ (1.4 mmol) dissolved in minimum amount of water, was added drop wise and stirred for 1–2 h. Upon completion of the reaction the mixture was diluted with EtOAc, washed with saturated aq. $NaHCO_3$ and then brine, dried over Na_2SO_4 and then evaporated to give pure lactone. Spectral data of representative lactone: (3-oxo-1,3,4,5-tetrahydronaphtho[1,2-*c*]furan-1-yl)-acetic acid methyl ester (**5a**): colourless crystalline solid. M. P. 130–132°C. FTIR (KBr, cm^{-1}): 2942, 1749, 1733, 1650, 1439, 1368, 1318, 1167, 1063, 1011, 766, 613. ^1H NMR ($CDCl_3$, 200 MHz): δ = 2.25–2.66 (m, 3H), 2.86–3.05 (m, 3H), 3.65 (s, 3H), 5.67–5.73 (m, 1H), 7.07–7.31 (m, 4H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 18.16, 27.85, 38.71, 52.23, 76.37, 123.90, 125.96, 127.15, 127.32, 128.92, 131.05, 137.81, 157.73, 169.79, 171.89. HRMS calcd for $C_{15}H_{15}O_4$ (MH^+) m/z = 259.0970, found m/z = 259.0967. Elemental anal. calcd for $C_{15}H_{14}O_4$: C, 69.76; H, 5.46. Found C, 69.62; H, 5.33%.

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