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One-pot synthesis of phthalides via regioselective intramolecular cyclization from *ortho*-alkynylbenzaldehydes

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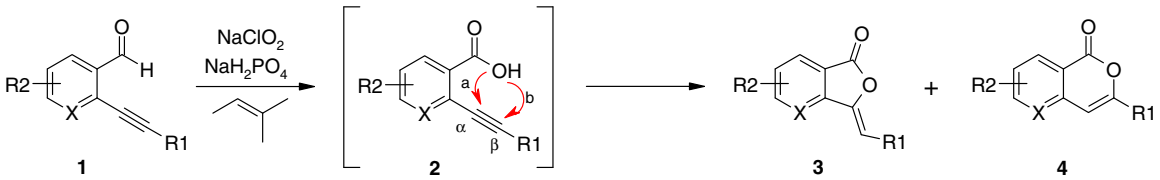
ABSTRACT

A one-pot synthesis of phthalides via an intramolecular 5-*exo-dig* cyclization of *ortho*-alkynylbenzaldehydes under mild $NaClO_2$ oxidation conditions is described.

Phthalides are an interesting class of structures with furan-2-(5*H*)-one skeletons which are often found in many natural products and biologically active compounds.[1,2] There has been considerable focus on their synthesis via intramolecular cyclization of *ortho*-alkynylbenzoic acid derivatives (**2**) in recent years.[3–7] Generally, metal complex-catalyzed intramolecular cyclizations of *ortho*-alkynylbenzoic acid derivatives (**2**) provide the desired furan-2-(5*H*)-one skeletons **3** and accompany the closely related isocoumarin **4** since both 5-*exo-dig* and 6-*endo-dig* cyclizations are preferable according to Baldwin's rule.[8] More recently, two groups reported a regioselective phthalide cyclization promoted by weak bases.[3,4] It is also known that acid-catalyzed cyclization often favored the isocoumarin formation.[9] Herein, we report a one-pot highly regioselective cyclization of *ortho*-alkynylbenzaldehydes under environmentally friendly sodium chlorite oxidative conditions that affords phthalides through an intramolecular 5-*exo-dig* pathway (Scheme 1).

During our work on converting a series of *ortho*-alkynylbenzaldehydes into their corresponding benzoic acids under very mild $NaClO_2$ oxidation conditions[10], we observed the formation of various amounts of phthalide products after the reactions were left for a period of time. We decided to investigate this transformation further and to study its synthetic scope (Scheme 1). The results of intramolecular phthalide cyclization from a series of *ortho*-alkynylbenzaldehydes (**1a**–**1o**)[11] are summarized in Table 1. In all cases, benzaldehydes were rapidly oxidized to the corresponding benzoic acids in the initial process. The subsequent intramolecular cyclization often required heating. The typical experimental procedure was carried out as follows: To a solution of the aldehyde (0.4 mmol) in a mixture of *t*-BuOH/THF/H_2O (6 mL, 2:1:3/v:v:v) at 0 °C were added NaH_2PO_4 (4.8 mmol), 2-methyl-2-butene (8 mmol), and followed by $NaClO_2$ (1 mmol). The mixture was allowed to warm to ambient temperature. The reaction mixture either continued stirring at the same temperature or heated at 50–90 °C over the indicated period of time until of the carboxylic acid intermediates were consumed.

We first examined the electronic influence of substituents on the backbone benzaldehyde ring (Table 1, entries 1–5). We were surprised to find that the corresponding carboxylic acid of unsubstituted *ortho*-benzaldehyde diphenylacetylene **1a** showed a significant lower reactivity toward the cyclization under the reaction conditions we attempted. Only 12% of the phthalide **3a** was isolated as the sole product along with 79% of the unreacted carboxylic acid **2a** after the reaction mixture was heated at 90 °C for 48 h. However, regioselective *5-exo-dig* cyclization of substrates **1b**–**1e** bearing both electron-donating and electron-withdrawing functional groups proceeded well under the given reaction conditions. Substrates with electron-rich moiety were found to be more



Scheme 1. One-pot intramolecular cyclization.

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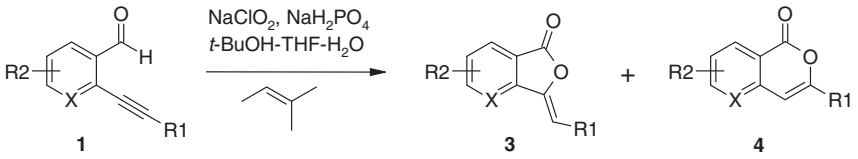
Table 1
One-pot intramolecular cyclization reactions[a]



Entry	1	R1	R2	X	Temp (°C)	Time (h)	3	Yield of 3[b] (%)
1[c]	**1a**	Ph	H	C	0–90	48	**3a**	12[d]
2	**1b**	Ph	5-MeO	C	0–25	14	**3b**	98
3	**1c**	Ph	4-F	C	0–50	14	**3c**	72
4	**1d**	Ph	6-F	C	0–50	14	**3d**	85
5	**1e**	Ph	H	N	0–50	24	**3e**	85[e]
6[c]	**1f**	*o*-CH_3–C_6H_4–	H	C	0–90	48	**3f**	20[f]
7	**1g**	*o*-CO_2Et–C_6H_4–	H	C	0–90	28	**3g**	65
8	**1h**	*o*-Cl–C_6H_4–	H	C	0–70	16	**3h**	53[g]
9	**1i**	*o*-CF_3–C_6H_4–	H	C	0–70	7	**3i**	94
10	**1j**	*p*-MeO–C_6H_4–	H	C	0–90	16	**3j**	84[h]
11	**1k**	2,4-Di-F–C_6H_4–	H	C	0–90	16	**3l**	72
12	**1l**	2,4-Di-MeO–C_6H_4–	H	C	0–90	28	**3m**	63[i]
13	**1m**	*t*-Bu	H	C	0–90	48	**3n**	0[j]
14	**1n**	H	H	C	0–70	14	**3o**	88

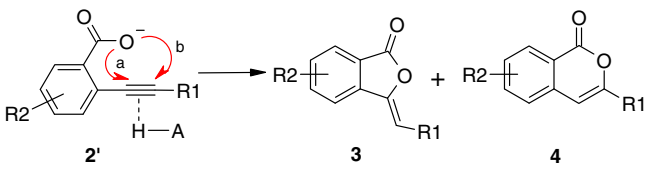
[a] All reactions were performed with aldehyde substrates (0.4 mmol), except for **1m** (0.15 mmol), $NaClO_2$ (1 mmol), NaH_2PO_4 (4.8 mmol) and 2-methyl-2-butene (8 mmol) at the indicated temperature and reaction time.
[b] Isolation yields.
[c] $NaClO_2$ (5 equiv), NaH_2PO_4 (24 equiv) and 2-methyl-2-butene (40 equiv) were used.
[d] The corresponding acid **2a** was isolated in 79% yield.
[e] Isocoumarin **4e** (7%) was observed in the product mixture.
[f] The corresponding carboxylic acid **2f** and isocoumarin **4f** were isolated in 72% and 4% yields, respectively.
[g] The corresponding carboxylic acid **2g** was isolated in 36% yield.
[h] Isocoumarin **4j** (14%) was observed in the product mixture.
[i] Isocoumarin **4k** (<5%) was observed in the product mixture.
[j] The corresponding carboxylic acid **2n** was isolated in 97% yield.

reactive toward the cyclization under milder reaction conditions. Benzaldehyde **1b** with a 5-MeO at the *para*-position to the alkyne moiety, efficiently led to phthalide **3b** as the exclusive product at 25 °C in 14 h.[12] Cyclizations of electron-poor substrates **1c**–**1e** were found to require heating at 50 °C (entries 3–5). Both 4-fluoro and 6-fluorobenzaldehydes **1c** and **1d** were able to transform into their corresponding phthalides **3c** and 3**d** in 72% and 85% yields, respectively. Conversion of pyridine **1e** into phthalide **3e** in 85% isolation yield and accompanied with the corresponding isocoumarin **4e** in 7% yield, required heating at 50 °C for 24 h (entry 5).

Next, we investigated the substitution effect of R1 group off the distal β-position of the carbon–carbon triple bond (Table 1, entries 6–14). Interestingly, we found that both *ortho*- and *para*-substitutions displayed a range of reactivity for this cyclization. We observed mostly modest to good yields with excellent regioselectivity for this 5-*exo*-*dig* phthalide cyclization which occurred at the α-position of the carbon–carbon triple bond regardless of the electronic nature of the substituents in R1 group (Table 1).

Both electronic and steric influences of *ortho*-substituents illustrated in the intramolecular cyclizations of a set of substrates (**1f**–**1i**) are summarized in Table 1 (entries 6–9). Cyclization of substrate **1f** bearing an electron-donating *ortho*-Me group was found to be sluggish which produced the desired phthalide **3f** in 20% yield and accompanied with 72% of the corresponding benzoic acid **2f** and 4% of isocoumarin **4f**, after the treatment with excess of reagents (5 equiv $NaClO_2$, 24 equiv NaH_2PO_4 and 40 equiv 2-methy-2-butene) at 90 °C for 48 h (entry 6). On the other hand, substrates bearing electron-withdrawing moieties at the *ortho*-position (**1g**–**1i**) underwent cyclization to provide the corresponding phthalides (**3g**–**3i**) in much higher yields at lower reaction temperature and in a shorter period of time (entries 7–9). To our delight, the 5-*exo*-*dig* cyclization of the most electronic deficient and sterically demanding **1i** with an *ortho*-CF_3 group proceeded exceptionally well to provide phthalide **3i** in 94% yield at 70 °C in 7 h (entry 9). Substrate **1j** bearing a *para*-MeO on the aromatic ring smoothly cyclized into phthalide **3j** in 84% yield and accompanied with isocoumarin **4j** in 14% yield (entry 10). Moreover, cyclizations of both 2,4-di-substituted substrates (**1k** and **1l**) bearing electron-withdrawing and electron-donating moieties on the distal aryl rings proceeded to give the corresponding phthalides **3k** and **3l** in 72% and 63% yields, respectively, although formation of **3l** with the 2,4-di-MeO substitution required almost twice longer reaction time at 90 °C than **3k** with the 2,4-di-fluoro moiety (entries 11 and 12). However, attempts to cyclize substrate **1m** bearing a distal bulky *t*-Bu group failed under the several reaction conditions while the corresponding benzoic acid **2m** was isolated as the sole product in 91% yield (entry 13). In the absence of such steric hindrance, cyclization of **1n** with a simple terminal alkyne proceeded smoothly to phthalide **3n** in 88% yield (entry 14).

The present intramolecular cyclization is expected to follow the proposed mechanism reported earlier, which requires an activation of the carbon–carbon triple bond by a Lewis acid (Scheme 2).[3,4] In all cases, formation of the 5-*exo*-*dig* phthalides is always preferential over the 6-*endo*-*dig* isocoumarin (Table 1). We postulate that both the reactivity and the regioselectivity of this intramolecular cyclization are influenced by the electronic nature of the carbon–carbon triple bond. Furthermore, this electronic influence depends



Scheme 2. Plausible mechanism for the intramolecular cyclization.

on the substitutions on both sides of the carbon–carbon triple bond, which polarizes the bond as described by the groups of Gevorgyan and co-workers[13] and Larock and co-workers.[6b] According to Gevorgyan and co-workers,[13] the *ortho*-benzoic acid moiety in intermediate **2′** produces the polarization effect on the carbon–carbon triple bond by making the α-position more positive. In the case of substrate **1b**, the electron-donating *para*-OMe group in the backbone benzoic acid ring further enhances the polarization of the carbon–carbon triple bond in a way that leads to more cationic character at the α-position than the β-position, thus facilitating the carboxylate nucleophilic attack at the more electrophilic position leading to the observed 5-*exo*-*dig* phthalide cyclization. This additional polarization effect by the *para*-OMe group significantly contributes cyclization reactivity and selectivity at a much lower temperature in comparison to the much less reactive unsubstituted **1a** (12% yield at 90 °C for 48 h).

In contrast, electronic effect of substituents on the distal β-position of carbon–carbon triple bond plays a different role in this intramolecular cyclization (entries 6–14). For the set of *ortho*-substituted substrates (entries **1f**–**1i**), it appears that these with the electron-deficient systems have a favorable effect on the outcome of this cyclization reaction. Despite having a bulkier *ortho*-CF_3 in **1i** relative to *ortho*-CH_3 in **1f**, the rate of cyclization of **1i** (94% yield) is clearly superior than **1f** (20% yield) at a lower reaction temperature and a shorter time (entries 6 and 9). According to Gevorgyan and co-workers,[13] electron-withdrawing and electron-donating substituents in the *ortho*-position of **1f** and **1i** induce different polarizations of the triple bond, as indicated by their opposite directions of dipole moment vectors. We anticipate that the dipole moment induced by the *ortho*-CF_3 group is in the same direction as the one from the carboxylate moiety, so that the overall constructive dipole moment further activates the triple bond for the intramolecular cyclization. On the other hand, electron-donating *ortho*-CH_3 group induces a dipole moment opposite to the carboxylate that leads to a less activated triple bond and the subsequent slow cyclization of **1f**.

In summary, we report a regioselective one-pot procedure to synthesize phthalides in good yields from readily available *ortho*-alkynylbenzaldehydes under mild $NaClO_2$ oxidation conditions. We also discuss the reactivity and scope of this intramolecular cyclization influenced by the electronic nature of substituents on both sides of the carbon–carbon triple bond.

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