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Organic-base-catalyzed synthesis of phthalides via highly regioselective intramolecular cyclization reaction

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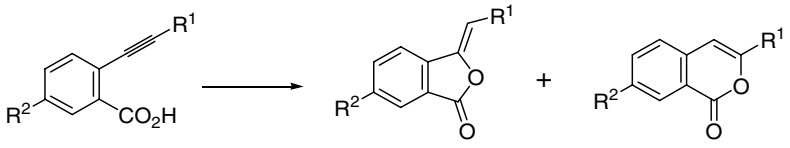
Abstract—The organic-base-catalyzed 5-*exo* intramolecular cyclization reaction of *o*-alkynylbenzoic acid produces the corresponding phthalide regioselectively in good to excellent yields. The method provides a practical access to the phthalides, an important class of biologically active molecules.

Phthalides **2** are an important class of oxygen-containing heterocycles often seen in naturally occurring and biologically active compounds.[1] One of the general routes for the synthesis of phthalides is the intramolecular cyclization reaction from *o*-alkynylbenzoic acid and its analogs (**1**) (Eq. 1). The drawback of this procedure is, it gives mixtures of phthalide **2** and isocoumarin **3** via 5-*exo* and 6-*endo* cyclization, respectively.[2–5] Therefore, the development of a highly regioselective cyclization route to phthalides has been paid much attention. Herein we report an intramolecular cyclization reaction of *o*-alkynylbenzoic acid **1** catalyzed by organic bases that affords phthalides in a highly regioselective manner.[6,7]



(1)

A preliminary experiment was conducted using 10 mol % DABCO (1,4-diazabicyclo[2,2,2]octane) as a catalyst in 1,4-dioxane at 100 °C (Table 1, entry 1). To our delight, 2-(2-phenylethynyl)benzoic acid **1a** (R^1 = Ph, R^2 = H, Eq. 1) was consumed completely within 6 h, and desired phthalide **2a** was obtained in an excellent yield without the formation of a detectable amount of isocoumarin **3a**. In addition, the geometry of **2a** was found to be (*Z*)-form exclusively. Among the organic base catalysts examined, DBU (1,8-diazabicyclo[5.4.0]-undec-7-ene) exhibited the highest catalytic activity (entry 3). Moreover, 5 mol % DBU was sufficient to promote completion of the reaction in 6 h even though the reaction temperature was lowered to 80 °C (entry 4). Solvent effect was also significant in the present intramolecular cyclization (entries 4–7). DBU displayed an excellent performance in highly polar solvents such as MeCN and DMSO (entries 6 and 7). Although both solvents reduced the reaction time markedly, MeCN was the best choice from a practical viewpoint (entry 6), as **2a** was isolated in a nearly quantitative manner (94% yield). It is interesting to note that a catalytic amount of potassium acetate also effectively promoted the 5-*exo* cyclization (entry 8). In contrast, a dramatic change in regioselectivity was observed in the presence of a catalytic amount of a strong acid, H_2SO_4, giving isocoumarin **3a** exclusively (entry 9).[6,8]

Keywords: Organic-base; Phthalide; Regioselective; Intramolecular cyclization.
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Table 1. Effects of catalysts and solvents[a]

Entry	Catalyst (mol %)	Solvent	Conditions[b]	**2a**/**3a**[c]
1	DABCO (10)	Dioxane	6 h, 100 °C	>95:<5
2	DMAP[d] (10)	Dioxane	24 h, 100 °C	>95:<5
3	DBU (10)	Dioxane	2 h, 100 °C	>95:<5
4	DBU (5)	Dioxane	6 h, 80 °C	>95:<5
5	DBU (5)	Toluene	6 h, 80 °C	>95:<5
6[e]	DBU (5)	MeCN	2 h, 80 °C	>95:<5
7	DBU (5)	DMSO	2 h, 80 °C	>95:<5
8	AcOK (10)	MeCN	6 h, 80 °C	>95:<5
9	H_2SO_4 (10)	Dioxane	12 h, 100 °C	<5:>95

[a] Unless otherwise noted, the intramolecular cyclization reaction of **1a** (R^1 = Ph, R^2 = H, 0.3 mmol) was conducted in the indicated solvent (0.6 mL) in the presence of a catalyst.
[b] Time required for completion of the reaction.
[c] Ratio was determined by ^{1}H NMR.
[d] DMAP = 4-(*N*,*N*-dimethylamino)pyridine.
[e] **2a** was isolated in 94% yield.

With the optimal conditions in hand, we next examined the scope and limitations of the present organic-base-catalyzed 5-*exo* cyclization with a series of *o*-alkynylbenzoic acids (**1**) (Table 2). Substrates bearing electron-donating or electron-withdrawing functional groups at the *para*-position of the terminal aromatic ring (R^1) as well as the sterically demanding 1-naphthyl substituent were tolerated for the reaction and gave the corresponding phthalides (**2b**, **2c**, and **2e**) in good to excellent yields (entries 2, 3, and 5). In contrast, the introduction of a substituent at the *ortho*-position of the terminal aromatic ring, **1d**, diminished the yield of **2d** and a considerable amount of isocoumarin **3d** was produced as well (entry 4). Substituents (R^2) introduced to the backbone aromatic ring also affected the mode of cyclization. The substrate bearing an electron-withdrawing acetyl group yielded isocoumarin **3f** although in a small amount. In contrast, an electron-donating methoxy group facilitated the exclusive formation of desired phthalide **2g**. To expand the applicability of the present 5-*exo* cyclization, we further examined a couple of terminal substituents attached to the alkynyl moiety.

Table 2. Scope of organic-base-catalyzed intramolecular cyclization reactions[a]

Entry	R^1	R^2	**1**	Time (h)	**2**	Yield[b] (%)
1	Ph	H	**1a**	2	**2a**	94
2	*p*-MeO–C_6H_4–	H	**1b**	4	**2b**	96
3	*p*-CF_3–C_6H_4–	H	**1c**	24	**2c**	80
4	*o*-MeO–C_6H_4–	H	**1d**	12	**2d**	57[c]
5	1-Naphthyl	H	**1e**	5	**2e**	97
6[d]	Ph	Ac	**1f**	12	**2f**	79[e]
7	Ph	MeO	**1g**	4	**2g**	99
8[f]	^{n}Pr	H	**1h**	12	**2h**	58[g]
9	2-Propenyl	H	**1i**	3	**2i**	65
10	H	H	**1j**	6	**2j**	83

[a] Unless otherwise noted, the reaction of **1** (0.3 mmol) was conducted in MeCN (0.6 mL) in the presence of DBU (15 μmol, 5 mol %) at 80 °C for the indicated time.
[b] Isolated yield.
[c] Isocoumarin **3d** was obtained in 23% yield.
[d] DMSO was used as solvent.
[e] Isocoumarin **3f** was obtained in 8% yield.
[f] DBU (10 mol %) was employed.
[g] Isocoumarin **3h** was obtained in 36% yield.

Unfortunately, the substitution of an aliphatic group, 2-(1-pentyl)benzoic acid **1h**, gave ca. 2:1 mixture of phthalide **2h** and isocoumarin **3h** (entry 8). However, the 5-*exo* selective cyclization was applicable to enyne **1i** and terminal alkyne **1j**, giving the corresponding phthalides in good yields without formation of isocoumarin derivatives (entries 9 and 10).

The present intramolecular cyclization is most probably initiated by the generation of a carboxylate anion intermediate via deprotonation of the carboxylic acid by the organic base catalyst (Fig. 1).[2b,6,8] The 5-*exo* cyclization of the carboxylate to the triple bond would be assisted by the conjugate acid of the organic base catalyst. Another possibility is that the carboxylic acid of substrate **1** on its own might intermolecularly aid the addition of the carboxylate anion, because a catalytic amount of potassium acetate also promotes the reaction effectively. Moreover, the substituent (R^2) effect of the backbone aromatic ring also suggests that the assistance by the acids is the key for the intramolecular cyclization (Table 2, entries 6 and 7). The electron-withdrawing substituent markedly retards the cyclization presumably due to the reduced electron density of the triple bond. The formation of a small amount of isocoumarin **3f** could be ascribed to the enhanced electrophilic nature at the β-position of the triple bond. In contrast, the introduction of electron-donating group to the backbone aromatic ring diminishes the electrophilic nature at the β-position of the triple bond and hence 5-*exo* cyclized product **2g** was formed exclusively.

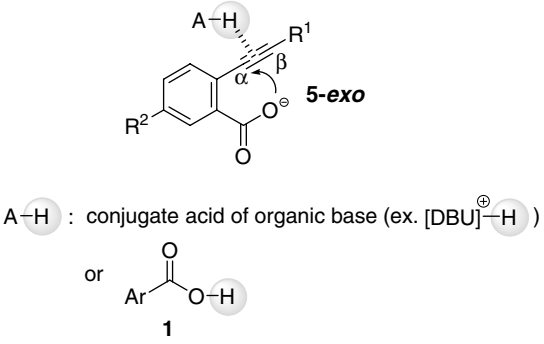

Figure 1. Plausible mechanism for the organic-base-catalyzed intramolecular cyclization.

In conclusion, we have developed an organic-base-catalyzed intramolecular cyclization reaction of *o*-alkynylbenzoic acid, leading to the 5-*exo* selective formation of phthalides in good to excellent yields.[9] The method provides a practical access to the phthalides, an important class of biologically active molecules. Further studies on the synthetic application are under way in our laboratory.

Acknowledgments

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6. During the preparation of this manuscript, Uchiyama et al. reported that the base- and acid-catalyzed alternative intramolecular cyclization of **1a** gave phthalide **2a** and isocoumarin **3a**, respectively. See: Uchiyama, M.; Ozawa, H.; Takuma, K.; Matsumoto, Y.; Yonehara, M.; Hiroya, K.; Sakamoto, T. *Org. Lett.* **2006**, *8*, 5517–5520.
7. Kundu et al. have also reported that the 5-*exo* selective cyclization of **1a** is promoted by NEt_3 to give phthalide **2a** in a low yield (30%). See Ref. 2b.
8. Trace amounts of **2a** and **3a** were obtained in the absence of the catalyst.
9. *Representative experimental procedure for the organic-base-catalyzed intramolecular cyclization leading to phthalide* **2**: To a MeCN solution (0.6 mL) of 2-(2-phenylethynyl)benzoic acid (**1a**) (66.7 mg, 0.3 mmol) was added DBU (2.2 μL, 15 μmol) under Ar atmosphere. The solution was stirred at 80 °C for 2 h. After the consumption of **1a**, the reaction mixture was cooled to room temperature, filtered through a short Florisil pad, and concentrated. The residue was purified by column chromatography (silica gel, *n*-hexane/AcOEt 50:1 to 5:1) to afford (*Z*)-3-(1-benzylidene)phthalide (**2a**) in 94% yield as a white solid (63 mg). ^{1}H NMR (400 MHz, $CDCl_3$): σ 6.41 (1H, s), 7.32 (1H, tt, $J = 7.5$, 1.2), 7.40–7.44 (2H, m), 7.53–7.57 (1H, m), 7.71–7.79 (2H, m), 7.84–7.86 (2H, m), 7.94–7.96 (1H, dt, $J = 7.5$, 1.0); ^{13}C NMR (100 MHz, $CDCl_3$): σ 106.99, 119.73, 123.35, 125.48, 128.32, 128.67, 129.67, 130.03, 133.01, 134.37, 140.51, 144.47, 166.88. These spectral data are consistent with previous reports.