PAPER

Check for updates

Cu₂O-mediated regio- and stereoselective one-pot synthesis of (*Z*)-3-ylidenephthalides from 2-iodobenzoic acids and terminal alkynes

Ahmed R. Ali [ID] [a,b] and Longqin Hu [ID] *[a,c]

A series of substituted (*Z*)-3-ylidenephthalides was synthesized from 2-iodobenzoic acids and various terminal alkynes in the presence of Cu₂O in DMF at 100–130 °C. Our copper(ɪ) oxide-catalyzed reaction requires no additional palladium, ligand, or base, making it an economical and efficient process. This optimized method is applicable to a range of 2-iodobenzoic acids and alkynes with diverse electronic, steric, and stability characteristics.

Introduction

Phthalides, particularly (*Z*)-3-ylidenephthalides, are crucial oxygen-containing heterocyclic compounds.[1] They're found in natural products like thunberginol F,[2] senkyunolide E,[3] and dactylicapnosine,[4] and in synthetic compounds with various biological activities, including anti-coagulant, anti-diabetic, and anti-HIV properties (Fig. 1).[5] C3-alkylphthalides, such as cytosporone E,[6] cryphonectric acid,[7] and fuscinarin,[8] are also important in complex natural product synthesis.[9] Furthermore, (*Z*)-3-ylidenephthalides are valuable synthetic intermediates;[10] for instance, benzylidenephthalide can be converted to phthalazinone, a key precursor to Olaparib, a drug for advanced ovarian cancer.[11] Phthalides also contain a furan-2-(5*H*)-one framework, a common feature in many biologically active molecules like rofecoxib.[12]

C–C coupling formation is crucial in the synthesis of pharmaceuticals and natural products.[13] The Sonogashira reaction is a widely used method for forming C(sp²)–C(sp) and (sp³)–C(sp) bonds through the cross-coupling of terminal alkynes with aryl/alkyl halides, typically using Pd/Cu or Pd complexes as catalysts.[14] To reduce costs, research has focused on replacing palladium with more affordable metals like nickel, iron, and copper. While copper, with ligands such as 1,10-phenanthroline, 1,3-diketone, and DABCO, can catalyze Pd-free Sonogashira reactions, these methods often require excessive amounts of ligands or elevated temperatures.[15]

As shown in Scheme 1, many methods exist for the preparation of (*Z*)-3-ylidenephthalides including (a) modified Perkin, Wittig or Julia reaction on phthalic anhydride;[16] (b) condensation of phthalic anhydride with phenylacetic acid;[17] (c) condensation of phthaloyl dichloride with 1,3-dicarbonyl compounds or silyl enol ethers;[18] (d) cyclization of 2-allyl- or 2-alkenylbenzoic acid derivatives;[19] (e) TSTU or AlCl₃-mediated intramolecular cyclization of 2-acylbenzoic acids;[20] (f) nickel/palladium-catalyzed isocyanide insertion on 2-haloacetophenones;[21] (g) CO insertion in palladium-catalyzed reactions of 2-halo or 2-triflyloxyacetophenones;[22] (h) Rh- or Pd-catalyzed tandem coupling and oxidative cyclization of benzoic acids with alkenes or terminal alkynes;[23] (i) Pd-free, base-free, Sonogashira-type coupling cyclization reaction on hypervalent iodine(ɪɪɪ) five-membered heterocycles;[24] (j) NaClO₂ or
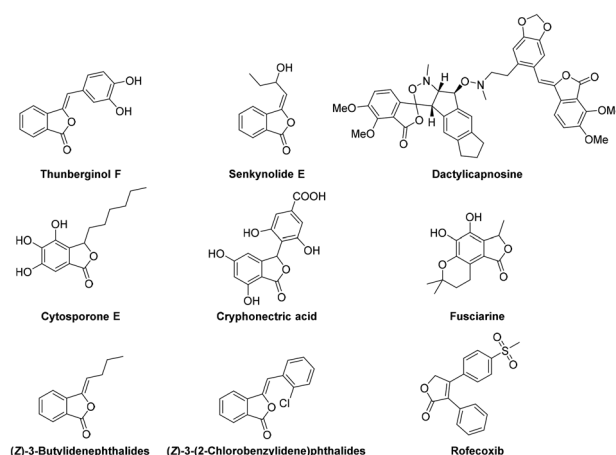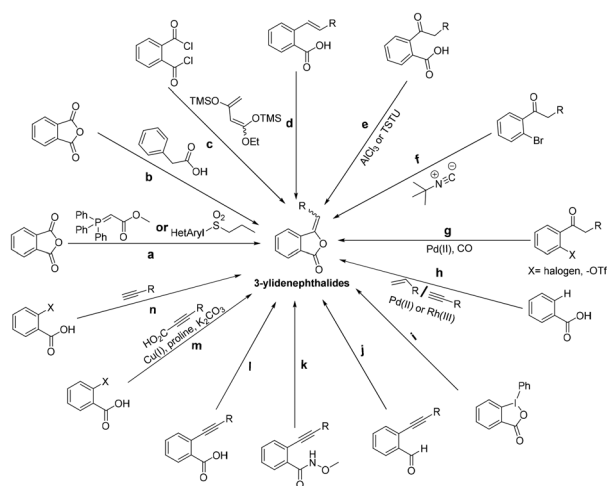
[a]Department of Medicinal Chemistry, Ernest Mario School of Pharmacy, Rutgers, The State University of New Jersey, 160 Frelinghuysen Road, Piscataway, New Jersey 08854, USA. E-mail: LongHu@pharmacy.rutgers.edu
[b]Department of Medicinal Chemistry, Faculty of Pharmacy, Mansoura University, Mansoura 35516, Egypt
[c]Rutgers Cancer Institute of New Jersey, New Brunswick, NJ 08901, USA

Fig. 1 Examples of natural or synthetic phthalides/furanones with biological activity.

This journal is © The Royal Society of Chemistry 2025

Org. Biomol. Chem., 2025, **23**, 7483–7490 | **7483**

Scheme 1 Synthetic pathways reported previously for 3-ylidenephthalides.

N-heterocyclic carbenes-mediated oxidative cyclization of 2-alkynylbenzaldehydes;[25] (k) domino gold-catalyzed cyclization and hydrolysis of 2-alkynyl-N-methoxybenzamides;[26] (l) cyclization of 2-alkynylbenzoic acids catalyzed by transition-metal (Pd, Cu, Ag, Au, or Rh),[3b,27] halogens,[28] or various base such as DBU, Et$_3$N and KOAc;[29] (m) copper-catalyzed tandem decarboxylative cross coupling–cyclization reactions of 2-iodo-benzoic acids and arylpropiolic acids;[30] and (n) transition-metal-catalyzed tandem coupling–cyclization reactions of 2-halobenzoic acids with terminal alkynes.[30b,31]

As shown in Fig. 2, metal-catalyzed intramolecular cyclizations of 2-alkynylbenzoic acids typically yield both the desired phthalide and the closely related isocoumarin scaffold. Baldwin's rules suggest that both 5-exo-dig and 6-endo-dig cyclization modes are favored, making selective phthalide synthesis challenging.[32] Regio- and stereocontrol are crucial for synthesizing pharmaceutically relevant molecules. Few reports describe regioselective phthalide (5-exo-dig) cyclization promoted by Cu^{2+}-NCS catalysis,[33] weak bases,[29a] and temperature control.[30b] While methods for preparing (Z)-3-ylidenephthalides exist, improved synthetic strategies are needed. Ideal methods would avoid expensive metal-catalysts, simplify purification procedures, minimize regio- or stereoisomerization, reduce side product formation, and provide high yields. Cost-effective coupling reagents are essential for practical industrial
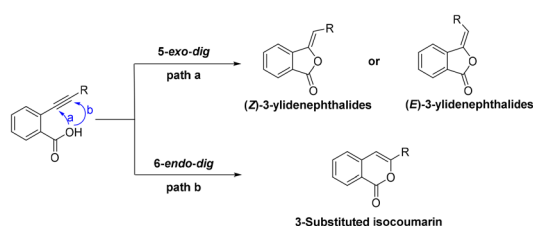
applications. Therefore, developing an efficient and economical protocol for the stereoselective synthesis of (Z)-3-ylidenephthalides remains important. Catalytic domino reactions offer a promising approach by minimizing solvent and reagent use, reaction time, purification steps, waste, and cost.

Building on our recent one-pot indole synthesis,[34] we envisioned a similar approach for the selective synthesis of (Z)-3-ylidenephthalides from 2-iodobenzoic acids (Fig. 2). We hypothesize that coupling between 2-iodobenzoic acids and terminal alkynes would generate 2-alkynylbenzoic acids *in situ*, which would then undergo Cu(ɪ)-mediated intramolecular cyclization to yield (Z)-3-ylidenephthalide. This method offers several significant advantages: (i) selective access to (Z)-3-ylidenephthalides from the similar starting materials by simply changing the nucleophile from methylsulfonamido to carboxylic acid; (ii) the commercial availability and reasonable cost of 2-iodobenzoic acids and their substituted analogs, along with established methods for selective *ortho*-iodination of benzoic acid derivatives;[35] (iii) a simple one-pot reaction and work-up procedure; and (iv) using a copper catalyst without ligands, bases or expensive palladium catalysts for C(sp)–C(sp^2) bond formation, enabling cost effective large scale production. To our knowledge, a Cu$_2$O-mediated tandem coupling–cyclization sequence for (Z)-3-ylidenephthalide synthesis has not been previously reported.
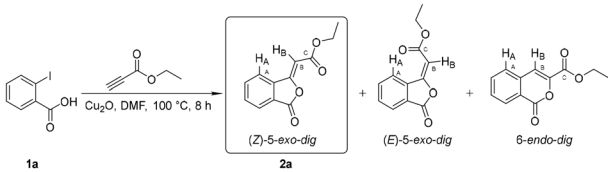
Results and discussion

Optimization of the reaction conditions

Building on our previous work on converting 2-iodo-N-mesylanilines to indoles under mild and economical coupling/cyclization conditions,[34] we explored extending this method to the synthesis of functionalized phthalides by replacing the methylsulfonamido group with a carboxylic acid group *ortho* to the iodo group. Inspired by the Castro–Stephens coupling, we chose a copper(ɪ)-catalyzed sequence. To avoid synthesizing and isolating copper(ɪ) acetylide as Castro–Stephens reaction, we sought a palladium-free one-pot synthesis of 3-ylidenephthalides in DMF. As Castro *et al.* demonstrated DMF's effectiveness for reactions between 2-iodobenzoic acid and copper(ɪ) acetylide,[27c,36] we adopted it in our initial screening.

Initially, we chose the coupling of 2-iodobenzoic acid (**1a**) with ethyl propiolate as a model reaction. As shown in Table 1, the reaction with copper(ɪ) oxide in DMF at 100 °C showed partial conversion of **1a** after 4 h (entry 1), as monitored by TLC and HPLC. Extending the reaction time to 6 and 8 h (entries 2 and 3) resulted in 90% conversion to the desired product **2a** as the sole product (Table 1, entry 3). (E)-5-Exo/6-endo products were not detected under the reaction conditions. Switching to different copper species, including Cu(0), Cu(ɪ) or Cu(ɪɪ) (entries 4–10), yielded no product; only starting material remained. Similarly, employing methanol, *tert*-butanol, THF, dioxane, 1,2-dimethoxyethane, acetonitrile, or toluene as solvents (entries 11–17) resulted in either moderate or no conversion of **1a**. The results confirmed DMF as the

Fig. 2 Two possible cyclization pathways leading to either 3-ylidenephthalides (5-exo-dig) or 3-substituted isocoumarins (6-endo-dig).

7484 | *Org. Biomol. Chem.*, 2025, **23**, 7483–7490

This journal is © The Royal Society of Chemistry 2025

Organic & Biomolecular Chemistry

Table 1 Screening of the reaction conditions[a]

Entry	Catalyst	Solvent	Time (h)	%conversion[b]
1	Cu$_2$O	DMF	4	62
2	Cu$_2$O	DMF	6	75
3	Cu$_2$O	DMF	8	90
4	CuCl	DMF	8	N.R.[c]
5	CuBr	DMF	8	N.R.
6	CuI	DMF	8	N.R.
7	Cu(OAc)$_2$	DMF	8	N.R.
8	CuSO$_4$	DMF	8	N.R.
9	Cu(OTf)$_2$	DMF	8	N.R.
10	Cu	DMF	8	N.R.
11	Cu$_2$O	MeOH	8	N.R.
12	Cu$_2$O	t-BuOH	8	13
13	Cu$_2$O	THF	8	23
14	Cu$_2$O	Dioxane	8	42
15	Cu$_2$O	DME	8	39
16	Cu$_2$O	MeCN	8	31
17	Cu$_2$O	PhMe	8	11

[a] Reactions were performed on a 0.1 mmol scale with the indicated catalyst (30 mol%) and solvent (0.5 mL) at 100 °C in sealed pressure-relief borosilicate glass vials. [b] Yields of conversion were based on HPLC. [c] No reaction.

optimal solvent, providing 90% conversion. Attempts to decrease catalyst loading, shorten reaction time, or change the solvent significantly diminished conversion.
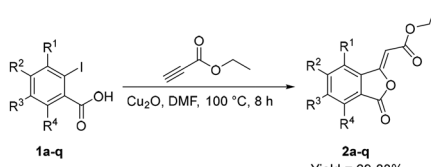
Spectral data for **2a**, compared with literature reports, confirmed the presence of an exocyclic double bond with Z geometry. ^{1}H and ^{13}C-NMR chemical shifts clearly distinguish between 5-exo-dig and 6-endo-dig cyclization, and between (Z)- and (E)-3-ylidenephthalides.[37] For 6-endo-dig cyclization leading to isocoumarin, H$_B$ resonates as a sharp singlet around 7.41 ppm.[38] In phthalides, H$_B$ appears at 6.39 ppm, consistent with the reported (Z)- and (E)-3-ylidenephthalides (6.51 and 6.33 ppm, respectively). The Z configuration is further supported by the chemical shift of the aromatic proton H$_A$. This proton is significantly deshielded in the E isomer (8.94 ppm) compared to the Z isomer (8.34 ppm).[37] Our observed chemical shift at 8.23 ppm strongly indicates the Z configuration. These data confirm the copper(I) oxide-mediated reaction of 2-iodobenzoic acid with ethyl propiolate yields (Z)-3-ylidenephthalides. Under our optimized conditions (30 mol% Cu$_2$O in DMF, without base or ligand), this process exhibits both regio- and stereoselectivity, generating (Z)-3-ylidenephthalides in high yield.

Effect of aryl substitutions on coupling of 2-iodobenzoic acids with ethyl propiolate

Having optimized our reaction conditions, we investigated the generality and scope of the method. Various electron donating

and electron withdrawing substituents at R^1, R^2, R^3 and R^4 were well tolerated. As shown in Table 2, substrates with electron-donating or electron-withdrawing groups at various positions on the aromatic ring generated the corresponding phthalides (**2b–2q**) in good to excellent yields with excellent stereoselectivity (entries 2–17). However, substrates with functional groups *ortho* to either the iodo- or the carboxylic acid group exhibited decreased reactivity, as demonstrated by lower yields in case of a fluoro group *ortho* to the iodo group (entry 2) or substituents adjacent to the free –COOH group (entries 14–17). Despite this steric hindrance, substrates **1b** and **1n–1q** still afforded the 5-exo-dig cyclization product in good yield.

Within Table 2, electron-donating methoxy groups (entries 6, 7 and 13) appeared to decrease reactivity compared to electron withdrawing groups (entries 3–5 and 8–10). Substrates with bromo substituents on the aromatic ring (entry 11) also showed reduced yields, likely due to potential C–C coupling at the C–Br bond. A key advantage of our metal-catalyzed 3-ylidenephthalide synthesis, starting from 2-iodobenzoic acid, is its regioselectivity compared to methods using benzoic acid derivatives. This is particularly relevant for *meta*-substituted benzoic acids like **1i–1m** (entries 9–13, Table 2), which would likely produce regioisomeric mixtures with other approaches. Using 2-iodo-5-substituted benzoic acid precursors, our method efficiently generates the desired 3-ylidenephthalides **2i–2m** in high yields (71–82%) *via* selective C–C bond formation with ethyl propiolate and subsequent C–O cyclization. Notably, our approach accommodates both electron-donating

Table 2 Scope of 3-ylidenephthalide derivatives from 2-iodobenzoic acids with ethyl propiolate[a]

Entry	Subs./prod.	R^1	R^2	R^3	R^4	Yield[b] (%)
1	**1a/2a**	–H	–H	–H	–H	82
2	**1b/2b**	–F	–H	–H	–H	69
3	**1c/2c**	–H	–F	–H	–H	83
4	**1d/2d**	–H	–Cl	–H	–H	82
5	**1e/2e**	–H	–NO$_2$	–H	–H	79
6	**1f/2f**	–H	–OCH$_3$	–H	–H	74
7	**1g/2g**	–H	–OCH$_3$	–OCH$_3$	–H	72
8	**1h/2h**	–H	–CF$_3$	–H	–H	83
9	**1i/2i**	–H	–H	–F	–H	80
10	**1j/2j**	–H	–H	–Cl	–H	76
11	**1k/2k**	–H	–H	–Br	–H	71
12	**1l/2l**	–H	–H	–CH$_3$	–H	82
13	**1m/2m**	–H	–H	–OCH$_3$	–H	74
14	**1n/2n**	–H	–H	–H	–F	71
15	**1o/2o**	–H	–H	–H	–Cl	72
16	**1p/2p**	–H	–H	–H	–CH$_3$	69
17	**1q/2q**	–H	–H	–H	–CF$_3$	70

[a] Reactions were carried out in pressure-relief borosilicate glass vials. [b] Isolated yields.

This journal is © The Royal Society of Chemistry 2025

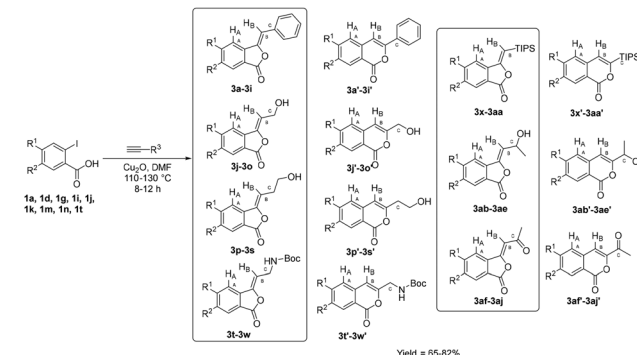*Org. Biomol. Chem.*, 2025, **23**, 7483–7490 | **7485**

and electron-withdrawing substituents, demonstrating its broad applicability for efficient and economical synthesis of multi-substituted 3-ylidenephthalides.

Effects of various alkynes on the formation of (Z)-3-ylidenephthalides

Having investigated the effect of substitutions on 2-iodobenzoic acids, we explored the scope and generality of this coupling–cyclization reaction method with various commercially available terminal alkynes. As shown in Table 3, using our optimized Cu_2O-catalyzed method, we prepared 3-ylidenephthalides bearing phenylidene (entries 1–9), hydroxyalkylidene (entries 10–19 and 28–31), Boc-aminoalkylidene (entries 20–23), TIPS-alkylidene (entries 24–27), and oxoalkylidene (entries 32–36) substituents at C-3 position of phthalide in good to excellent yields. Our approach directly converts readily available alkynes and 2-iodobenzoic acids into the desired (Z)-3-ylidenephthalides in 53–81% yield, in contrast to Castro–Stephens coupling, which primarily uses phenylacetylene and requires a separate step to generate copper(I) acetylide.

Table 3 Scope of diverse alkynes used to synthesize 3-ylidenephthalides *via* our Cu_2O-catalyzed method[a]

Entry	Subs./prod.	R^1	R^2	R^3	Reaction temperature (°C)	Time (h)	Yield[b] (%)
1	**1a/3a**	–H	–H	–Ph	110	8	81
2	**1i/3b**	–H	–F				79
3	**1j/3c**	–H	–Cl				79
4	**1k/3d**	–H	–Br				70
5	**1m/3e**	–H	–CH₃				79
6	**1n/3f**	–H	–OCH₃				75
7	**1g/3g**	–OCH₃	–OCH₃				71
8	**1d/3h**	–Cl	–H				71
9	**1t/3i**	–Br	–H				71
10	**1a/3j**	–H	–H	–CH₂OH	120	12	73
11	**1k/3k**	–H	–Br				63
12	**1m/3l**	–H	–CH₃				70
13	**1n/3m**	–H	–OCH₃				62
14	**1g/3n**	–OCH₃	–OCH₃				61
15	**1d/3o**	–Cl	–H				60
16	**1a/3p**	–H	–H	–CH₂CH₂OH	120	12	75
17	**1m/3q**	–H	–CH₃				72
18	**1n/3r**	–H	–OCH₃				68
19	**1g/3s**	–OCH₃	–OCH₃				71
20	**1a/3t**	–H	–H	–CH₂NH–Boc	120	12	78
21	**1m/3u**	–H	–CH₃				81
22	**1n/3v**	–H	–OCH₃				73
23	**1g/3w**	–OCH₃	–OCH₃				73
24	**1a/3x**	–H	–H	–TIPS	130	18	77
25	**1m/3y**	–H	–CH₃				76
26	**1n/3z**	–H	–OCH₃				72
27	**1g/3aa**	–OCH₃	–OCH₃				71
28	**1a/3ab**	–H	–H	–CH₂CHOHCH₃	120	12	71
29	**1m/3ac**	–H	–CH₃				61
30	**1n/3ad**	–H	–OCH₃				58
31	**1t/3ae**	–Br	–H				53
32	**1a/3af**	–H	–H	–COCH₃	100	8	78
33	**1i/3ag**	–H	–F				80
34	**1j/3ah**	–H	–Cl				79
35	**1m/3ai**	–H	–CH₃				79
36	**1n/3aj**	–H	–OCH₃				72

[a] All reactions were carried out in pressure-relief borosilicate glass vials at the temperature and for the duration indicated. [b] Isolated yields.

The alkynes employed showed excellent compatibility with various aryl substituents, both electron-donating or electron-withdrawing. While the synthesis of hydroxyalkylidene derivatives (entries 10–19 and 28–31) has received limited attention in the literature, this work, to our knowledge, represents the first synthesis of Boc-aminoalkylidene (entries 20–23) and oxoalkylidene (entries 32–36) derivatives. Furthermore, it is the first instance of introducing a protected acetylene moiety (entries 24–27) to 2-iodobenzoic acid substrates using a non-palladium catalyzed method. Our simplified tandem reaction efficiently generated (Z)-3-ylidenephthalides **3a–3aj** (Table 3). These products, possessing diverse substituents at the 3-position, are valuable building blocks for more complex phthalide-based compounds.

Coupling with phenylacetylene proceeded smoothly, exclusively yielding the (Z)-5-exo-dig products (**3a–3i**). The structure of (Z)-3-benzylidenephtahalide (**3a**) was confirmed by extensive 1D and 2D NMR analysis (COSY, HSQC, HMBC, NOESY and APT; SI). A peak at 166.3 ppm, characteristic of 5-membered lactone (more deshielded than 6-membered isocoumarin lactone), was observed in its ^{13}C-NMR. The H_B proton at 6.92 ppm showed four HMBC correlations: two with quaternary carbons at 140.1 and 144.2 ppm, and two with tertiary aromatic carbons at 129.7 and 130.3 ppm. The latter two peaks, assigned to the phenyl ring from phenylacetylene, confirm the formation of a 3-ylidenephthalide, not an isocoumarin. The Z configuration was assigned based on NOESY spectra (SI), which showed two correlations between the H_B proton and two doublet signals. Reactions with phenylacetylene generally proceeded well (entries 1–9, Table 3), with higher yields observed for 2-iodobenzoic acids with electron-withdrawing groups compared to those with electron-donating groups.

Phthalides with 3-hydroxyalkylidene substituent (entries 10–19 and 28–31, Table 3) were obtained in lower yields compared to those derived from alkynes bearing electron withdrawing groups (e.g., ethyl propiolate or phenylacetylene). This suggests that our coupling/cyclization is more efficient with electron-deficient alkynes. Within the 3-hydroxyalkylidenephthalide series, higher yields were still observed with 2-iodobenzoic acids bearing electron-withdrawing groups. The structures were confirmed by 1D and 2D NMR analysis (SI). A COSY correlation between H_B and neighboring aliphatic protons ruled out isocoumarin (6-endo-dig) formation. Furthermore, the vinylic H_B proton showed 3–4 HMBC correlations, confirming the installation of the hydroxyalkylidene moiety and phthalide ring formation. A NOESY correlation between H_A and H_B also supported the assigned Z-isomer structure.

Coupling with N-Boc-propargylamine (entries 20–23, Table 3) gave slightly higher yields than the 3-hydroxyalkylidenephthalides. This may be attributed to the masked hydroxyl group and protected amine, which could reduce chelation with the Cu(ɪ) species, a potential factor contributing to lower yields in the 3-hydroxyalkylidenephthalides synthesis. Trimethylsilylacetylene did not afford the desired phthalide. However, using the more stable triisopropylsilylacetylene,

corresponding products were obtained in 71–77% yields without desilylation (entries 24–27, Table 3). The structure of **3x** (entry 24) was confirmed by 1D and 2D NMR analysis (SI). Two HMBC correlations were observed between H_B proton and the isopropylene and quaternary aromatic carbons. A NOESY signal between H_A and H_B protons confirmed the Z-configuration.

Coupling with 3-butyn-2-one smoothly generated the corresponding (Z)-3-oxopropylidnephthalides in good to high yields (72–80%) with excellent stereoselectivity. The structure and configuration of compound **3af** (entry 32, Table 3) were confirmed by 2D NMR (HMBC and NOESY; SI). Notably, our optimized method generates 3-functionalized-ylidenephthalides in good to excellent yields, accommodating both electron-rich and electron-poor alkynes. The mild reaction conditions also enable the synthesis of phthalide cores with acid- or base-sensitive functionalities at the 3-position, as exemplified by the Boc protecting groups (entries 20–23, Table 3) and ester-containing 3-ylidenephthalides (Table 2).

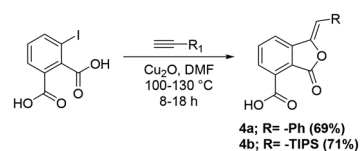### Coupling/cyclization of diacidic substrates

Having optimized the reaction conditions, we investigated a series of alternative substrates possessing an additional free carboxylic acid group. Typical heteroannulation reactions involving Sonogashira coupling and cyclization are performed under basic conditions, which can be problematic in the presence of free acidic groups. However, as shown in Scheme 2, substrates with an additional free carboxylic acid group on the aryl ring (beside the one ortho to the iodo group) successfully generated the corresponding (Z)-3-ylidenephthalides in good to high yield with excellent stereoselectivity. This is, to our knowledge, the first example of such substrates, bearing ionizable groups, being coupled to furnish (Z)-3-ylidenephthalides.

Scalability

To assess the scalability, we performed a gram-scale synthesis of (Z)-3-ylidenephthalide **2a** from 2-iodobenzoic acid (**1a**). This demonstrated the potential of our Cu₂O-mediated method for larger scale applications. The coupling and cyclization of **1a** (1 g, 4.03 mmol) with ethyl propiolate (0.4 mL, 4.03 mmol) in 6 mL of DMF, after heating in the presence of Cu₂O (30 mol%) at 100 °C for 8 h, afforded **2a** in 84% isolated yield.
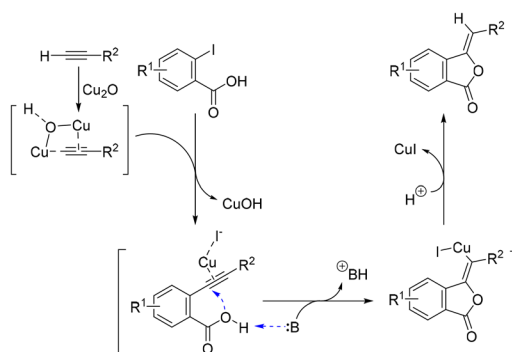
Proposed reaction mechanism

Based on these results and our previous studies on the same catalytic system,[35] we propose the following mechanism as

Scheme 2 Coupling/cyclization of a diacidic substrate with alkynes using our Cu₂O-catalyzed method.

This journal is © The Royal Society of Chemistry 2025

Org. Biomol. Chem., 2025, **23**, 7483–7490 | **7487**

Scheme 3 Proposed mechanism for the formation of (Z)-3-ylide-nephthalides from 2-iodobenzoic acids and alkynes in the presence of Cu_2O.

depicted in Scheme 3 for the formation of (Z)-3-ylidenephtha-lides. The catalytic cycle initiates with the coordination of the terminal alkyne to the heterogeneous Cu_2O catalyst surface. At the Cu(I) sites on this surface, the alkyne undergoes deprotona-tion. This step is facilitated by the intrinsic basicity of surface oxygen atoms or trace CuOH species present on the catalyst, leading to the formation of a surface-bound Cu–alkynyl species. Although DMF decomposition at high temperatures can produce small amounts of Me_2NH, which might aid alkyne deprotona-tion, Cu_2O's intrinsic basicity is sufficient, as evidenced by partial conversion in toluene (Table 1, entry 17). Our base-free conditions (100–130 °C) offer a simpler and more cost-effective alternative to base-mediated room-temperature methods, while also avoiding side reactions with acid-sensitive substrates. For safety, reactions were conducted below DMF's decomposition threshold (~150 °C) in pressure-relief borosilicate vials within a well-ventilated fume hood.

Subsequently, the surface-bound Cu–alkynyl species partici-pates in a C–C coupling with an aryl iodide (Ar–I), which is also adsorbed and activated on the Cu_2O surface via the C–I cleavage. Specifically, 2-iodobenzoic acid reacts with the Cu_2O surface through coordination of its ortho-carboxylic acid group to Cu(I) sites. This spatial arrangement positions the C–I bond of 2-iodo-benzoic acid in close proximity to surface-bound Cu–alkynyl species, enabling an insertion reaction. This entire process occurs on the catalyst surface, leveraging the unique environment of neighboring Cu and O sites within Cu_2O to stabilize the tran-sition state. This leads to the formation of aryl–Cu–alkynyl surface-bound intermediates followed by reductive elimination to yield the 2-alkynylbenzoic acid intermediate.

The coordination of the carboxylic acid plays a crucial role in directing the subsequent cyclization step. The observed 5-exo-dig cyclization is attributed to the proximity of the co-ordinated carboxylate oxygen to the Cu-activated triple bond. Adjacent copper(I) species further stabilize transition state on the surface, rendering the alkyne more electrophilic and facili-tating nucleophilic attack by the carboxylic group, resulting in the formation of the five-membered phthalide ring. This pre-ference for 5-exo-dig over 6-endo-dig cyclization arises from the

geometric constraints imposed by the carboxylic acid's coordi-nation to Cu_2O, which favors the closure of the smaller five-membered ring. This observation is consistent with a previous report by Uchiyama and co-workers,[29a] demonstrating that such cyclization reactions of 2-alkynyl-benzoic acid under basic conditions favor 5-exo-dig phthalide formation.

Unlike the method developed by Kumar et al.,[30b] which reported poor regioselectivity for meta-substituted 2-iodoben-zoic acids due to competing 6-endo-dig cyclization, our Cu_2O-mediated protocol exclusively affords (Z)-3-ylidenephthalides (5-exo-dig) in high yields (71–82%, Table 2, entries 9–13). This enhanced regioselectivity is likely due to the Cu_2O surface's ability to direct cyclization via carboxylate coordination, thus preventing isocoumarin formation. The Cu_2O surface stabil-izes the transition state, ensuring efficient phthalide pro-duction. Unlike other copper species tested, Cu_2O's superiority as a catalyst in our methodology likely stems from its hetero-geneous surface featuring Cu(I) sites and inherent mild basi-city. This combination effectively facilitates alkyne deprotona-tion, stabilizes the C–C coupling transition state, and pro-motes subsequent cyclization. DMF was proved to be the best solvent with 90% conversion (entry 3), while very little or no conversion was observed for solvents such as methanol, THF, and toluene (entries 11–17).

The cyclized Cu–carbon intermediate undergoes cleavage via protonation to release (Z)-3-ylidenephthalide. Potential proton sources include residual water, carboxylic acid, or solvent-derived species. This protonation regenerates the Cu_2O surface in its Cu(I) form, allowing the catalytic cycle to con-tinue. This overall process efficiently generates (Z)-3-ylide-nephthalides with diverse functionalities at the 3-position, without detectable intermediates or by-products, consistent with a concerted, surface-mediated mechanism.

In summary, we have developed a simple and efficient method for the synthesis of (Z)-3-ylidenephthalides from readily available 2-iodobenzoic acids and diverse terminal alkynes. This process provides one of the simplest routes to this valuable class of phthalide analogs, utilizing copper(I) oxide as a catalyst in DMF, without the need for palladium, bases, or ligands. This user-friendly method offers a practical approach to a variety of 3-ylidenephthalides via a tandem coupling/cyclization sequence, without requiring rigorous exclusion of moisture or air. A series of diversely substituted 3-functionalized phthalides was obtained via 5-exo-dig cycliza-tion, exclusively yielding the Z-configuration. Characterized by mild reaction conditions and good to excellent yields, this pro-tocol should be highly attractive for large scale industrial appli-cations and medicinal chemistry efforts.

Experimental section

General procedure for copper(I)-mediated coupling and cyclization reaction

A mixture of 2-iodobenzoic acid (1.0 equivalent), alkyne (1–1.5 equivalents), and copper(I) oxide (0.3 equivalents) in DMF

(1.5 mL per 1 mmol of 2-iodobenzoic acid) was heated to 100–130 °C for 8–18 h within a well-ventilated fume hood. After cooling to room temperature, the reaction mixture was quenched with either saturated NH_4Cl (for *N*-Boc-propargylamine) or 1 N HCl and extracted with ethyl acetate. The combined organic extracts were dried over anhydrous Na_2SO_4, concentrated under reduced pressure, and the resulting residue was purified by flash chromatography using an ethyl acetate/hexane gradient to afford the desired product.

Author contributions

A. R. A. proposed and optimized the synthetic method, synthesized and characterized all compounds, and wrote the initial draft of the manuscript. L. H. secured funding and supervised the project. All authors discussed the experiments, commented and edited the manuscript.

Conflicts of interest

The authors declare no competing financial interest.

Data availability

The data supporting this article have been included as part of the SI.

Supplementary information containing experimental details and characterization data of the new compounds as well as copies of ^1H and ^{13}C NMR spectra with HRMS data of all new compounds are available. See DOI: https://doi.org/10.1039/d5ob00808e.

References

1 (a) L. M. Bedoya, E. del Olmo, R. Sancho, B. Barboza, M. Beltran, A. E. Garcia-Cadenas, S. Sanchez-Palomino, J. L. Lopez-Perez, E. Munoz, A. San Feliciano and J. Alcami, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 4075–4079; (b) T. H. Chou, I. S. Chen, T. L. Hwang, T. C. Wang, T. H. Lee, L. Y. Cheng, Y. C. Chang, J. Y. Cho and J. J. Chen, *J. Nat. Prod.*, 2008, **71**, 1692–1695.

2 (a) M. Yoshikawa, E. Uchida, N. Chatani, N. Murakami and J. Yamahara, *Chem. Pharm. Bull.*, 1992, **40**, 3121–3123; (b) K. Umehara, M. Matsumoto, M. Nakamura, T. Miyase, M. Kuroyanagi and H. Noguchi, *Chem. Pharm. Bull.*, 2000, **48**, 566–567.

3 (a) T. Naito, K. Niitsu, Y. Ikeya, M. Okada and H. Mitsuhashi, *Phytochemistry*, 1992, **31**, 1787–1789; (b) F. Bellina, D. Ciucci, P. Vergamini and R. Rossi, *Tetrahedron*, 2000, **56**, 2533–2545; (c) F. Bohlmann, M. A. Metwally and J. Jakupovic, *Phytochemistry*, 1984, **23**, 1975–1977.

4 G.-L. Zhang, G. Rücker, E. Breitmaier, M. Nieger, R. Mayer and C. Steinbeck, *Phytochemistry*, 1995, **40**, 299–305.

5 (a) G. Ortar, A. Schiano Moriello, E. Morera, M. Nalli, V. Di Marzo and L. De Petrocellis, *Bioorg. Med. Chem. Lett.*, 2013, **23**, 5614–5618; (b) V. Rukachaisirikul, A. Rodglin, Y. Sukpondma, S. Phongpaichit, J. Buatong and J. Sakayaroj, *J. Nat. Prod.*, 2012, **75**, 853–858; (c) H. Yang, G. Y. Hu, J. Chen, Y. Wang and Z. H. Wang, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 5210–5213.

6 S. F. Brady, M. M. Wagenaar, M. P. Singh, J. E. Janso and J. Clardy, *Org. Lett.*, 2000, **2**, 4043–4046.

7 A. Arnone, G. Assante, G. Nasini, S. Strada and A. Vercesi, *J. Nat. Prod.*, 2002, **65**, 48–50.

8 K. Yoganathan, C. Rossant, S. Ng, Y. Huang, M. S. Butler and A. D. Buss, *J. Nat. Prod.*, 2003, **66**, 1116–1117.

9 (a) M. L. Patil, H. B. Borate, D. E. Ponde and V. H. Deshpande, *Tetrahedron*, 2002, **58**, 6615–6620; (b) D. Mal and P. Pahari, *Chem. Rev.*, 2007, **107**, 1892–1918.

10 (a) H. S. Ibrahim, W. M. Eldehna, H. A. Abdel-Aziz, M. M. Elaasser and M. M. Abdel-Aziz, *Eur. J. Med. Chem.*, 2014, **85**, 480–486; (b) A. Quemener, M. Maillasson, L. Arzel, B. Sicard, R. Vomiandry, E. Mortier, D. Dubreuil, Y. Jacques, J. Lebreton and M. Mathe-Allainmat, *J. Med. Chem.*, 2017, **60**, 6249–6272; (c) R. Karmakar, P. Pahari and D. Mal, *Chem. Rev.*, 2014, **114**, 6213–6284.

11 Z. Chen, S. Wang, K. Liu, R. Zhang, Q. Li, W. Bian, R. Qiao and C. Li, *ACS Omega*, 2022, **7**, 6313–6321.

12 (a) D. Riendeau, M. D. Percival, S. Boyce, C. Brideau, S. Charleson, W. Cromlish, D. Ethier, J. Evans, J. P. Falgueyret, A. W. Ford-Hutchinson, R. Gordon, G. Greig, M. Gresser, J. Guay, S. Kargman, S. Leger, J. A. Mancini, G. O'Neill, M. Ouellet, I. W. Rodger, M. Therien, Z. Wang, J. K. Webb, E. Wong, C. C. Chan, *et al.*, *Br. J. Pharmacol.*, 1997, **121**, 105–117; (b) C.-S. Li, W. C. Black, C. Brideau, C. Chi Chung, S. Charleson, W. A. Cromlish, D. Claveau, J. Y. Gauthier, R. Gordon, G. Greig, E. Grimm, J. Guay, C. K. Lau, D. Riendeau, M. Thérien, D. M. Visco, E. Wong, X. Lijing and P. Prasit, *Bioorg. Med. Chem. Lett.*, 1999, **9**, 3181–3186; (c) Y. Leblanc, P. Roy, S. Boyce, C. Brideau, C. C. Chan, S. Charleson, R. Gordon, E. Grimm, J. Guay, S. Léger, C. S. Li, D. Riendeau, D. Visco, Z. Wang, J. Webb, L. J. Xu and P. Prasit, *Bioorg. Med. Chem. Lett.*, 1999, **9**, 2207–2212.

13 (a) L. Yin and J. Liebscher, *Chem. Rev.*, 2007, **107**, 133–173; (b) M. A. Andrade and L. Martins, *Molecules*, 2020, **25**, 5506; (c) K. C. Nicolaou, P. G. Bulger and D. Sarlah, *Angew. Chem., Int. Ed.*, 2005, **44**, 4442–4489.

14 (a) K. Sonogashira, Y. Tohda and N. Hagihara, *Tetrahedron Lett.*, 1975, **16**, 4467–4470; (b) R. Chinchilla and C. Najera, *Chem. Rev.*, 2007, **107**, 874–922; (c) R. Chinchilla and C. Najera, *Chem. Soc. Rev.*, 2011, **40**, 5084–5121.

15 (a) M. B. Thathagar, J. Beckers and G. Rothenberg, *Green Chem.*, 2004, **6**, 215–218; (b) J. H. Li, J. L. Li, D. P. Wang, S. F. Pi, Y. X. Xie, M. B. Zhang and X. C. Hu, *J. Org. Chem.*, 2007, **72**, 2053–2057; (c) F. Monnier, F. Turtaut, L. Duroure and M. Taillefer, *Org. Lett.*, 2008, **10**, 3203–3206;

This journal is © The Royal Society of Chemistry 2025

Org. Biomol. Chem., 2025, **23**, 7483–7490 | 7489

(d) H. Plenio, *Angew. Chem., Int. Ed.*, 2008, **47**, 6954–6956; (e) M. Carril, A. Correa and C. Bolm, *Angew. Chem., Int. Ed.*, 2008, **47**, 4862–4865; (f) E. Zuidema and C. Bolm, *Chem. – Eur. J.*, 2010, **16**, 4181–4185.

16 (a) M. M. Kayser, K. L. Hatt and D. L. Hooper, *Can. J. Chem.*, 1992, **70**, 1985–1996; (b) J. Zhu and M. M. Kayser, *Synth. Commun.*, 1994, **24**, 1179–1186; (c) D. T. Mowry, E. L. Ringwald and M. Renoll, *J. Am. Chem. Soc.*, 2002, **71**, 120–122; (d) N. Dussart, H. V. Trinh and D. Gueyrard, *Org. Lett.*, 2016, **18**, 4790–4793.

17 J. Munin, E. Quezada, D. Vina, E. Uriarte, G. L. Delogu and J. Gil-Longo, *Future Med. Chem.*, 2019, **11**, 179–191.

18 (a) S. N. Naik, B. Pandey and N. R. Ayyangar, *Synth. Commun.*, 1988, **18**, 625–632; (b) K. Maruyama and A. Osuka, *J. Org. Chem.*, 2002, **45**, 1898–1901; (c) P. Langer, S. Mkrtchyan, Z. Chilingaryan, G. Ghazaryan, R. Dede, N. Rasool, M. Rashid, A. Villinger, H. Görls, G. Karapetyan, T. Ghochikyan and A. Saghiyan, *Synthesis*, 2011, 2281–2290.

19 (a) N. Yasmin and J. K. Ray, *RSC Adv.*, 2013, **3**, 25631–25635; (b) J. He, J. Zhang, X. Li, H. Shi and Y. Du, *Chem. Commun.*, 2022, **58**, 9096–9099.

20 (a) X. Wang, G. Li, X. Zhang, Z. Feng, J. Jiang, Y. Yang and P. Zhang, *Tetrahedron Lett.*, 2020, **61**, 151734; (b) X. He and F. Xue, *Tetrahedron Lett.*, 2014, **55**, 1956–1958.

21 (a) X.-D. Fei, T. Tang, Z.-Y. Ge and Y.-M. Zhu, *Synth. Commun.*, 2013, **43**, 3262–3271; (b) X. D. Fei, Z. Y. Ge, T. Tang, Y. M. Zhu and S. J. Ji, *J. Org. Chem.*, 2012, **77**, 10321–10328.

22 (a) P. G. Ciattini, G. Mastropietro, E. Morera and G. Ortar, *Tetrahedron Lett.*, 1993, **34**, 3763–3766; (b) Q. Yuan, Z. B. Chen, F. L. Zhang and Y. M. Zhu, *Org. Biomol. Chem.*, 2017, **15**, 1628–1635.

23 (a) G. Danoun, P. Mamone and L. J. Goossen, *Chem. – Eur. J.*, 2013, **19**, 17287–17290; (b) D. Nandi, D. Ghosh, S. J. Chen, B. C. Kuo, N. M. Wang and H. M. Lee, *J. Org. Chem.*, 2013, **78**, 3445–3451; (c) M. Zhang, H. J. Zhang, T. Han, W. Ruan and T. B. Wen, *J. Org. Chem.*, 2015, **80**, 620–627; (d) Y. Liu, Y. Yang, Y. Shi, X. Wang, L. Zhang, Y. Cheng and J. You, *Organometallics*, 2016, **35**, 1350–1353; (e) W.-J. Han, F. Pu, J. Fan, Z.-W. Liu and X.-Y. Shi, *Adv. Synth. Catal.*, 2017, **359**, 3520–3525.

24 A. A. Almasalma and E. Mejía, *Eur. J. Org. Chem.*, 2018, 188–195.

25 (a) J. Li, E. Chin, A. S. Lui and L. Chen, *Tetrahedron Lett.*, 2010, **51**, 5937–5939; (b) J. H. Park, S. V. Bhilare and S. W. Youn, *Org. Lett.*, 2011, **13**, 2228–2231.

26 D. Ding, T. Mou, J. Xue and X. Jiang, *Chem. Commun.*, 2017, **53**, 5279–5282.

27 (a) H.-Y. Liao and C.-H. Cheng, *J. Org. Chem.*, 2002, **60**, 3711–3716; (b) H. Sashida, *Synthesis*, 1999, 1145–1148; (c) C. E. Castro, E. J. Gaughan and D. C. Owsley, *J. Org. Chem.*, 2002, **31**, 4071–4078; (d) E. Marchal, P. Uriac, B. Legouin, L. Toupet and P. v. d. Weghe, *Tetrahedron*, 2007, **63**, 9979–9990; (e) B. Y. W. Man, A. Knuhtsen, M. J. Page and B. A. Messerle, *Polyhedron*, 2013, **61**, 248–252; (f) R. Mancuso, C. S. Pomelli, P. Chiappetta, K. F. Gioia, A. Maner, N. Marino, L. Veltri, C. Chiappe and B. Gabriele, *J. Org. Chem.*, 2018, **83**, 6673–6680.

28 M. Biagetti, F. Bellina, A. Carpita, P. Stabile and R. Rossi, *Tetrahedron*, 2002, **58**, 5023–5038.

29 (a) M. Uchiyama, H. Ozawa, K. Takuma, Y. Matsumoto, M. Yonehara, K. Hiroya and T. Sakamoto, *Org. Lett.*, 2006, **8**, 5517–5520; (b) C. Kanazawa and M. Terada, *Tetrahedron Lett.*, 2007, **48**, 933–935.

30 (a) T. Ponpandian and S. Muthusubramanian, *Tetrahedron Lett.*, 2012, **53**, 4248–4252; (b) M. R. Kumar, F. M. Irudayanathan, J. H. Moon and S. Lee, *Adv. Synth. Catal.*, 2013, **355**, 3221–3230.

31 (a) L. Zhou and H.-F. Jiang, *Tetrahedron Lett.*, 2007, **48**, 8449–8452; (b) D. Rambabu, G. P. Kumar, B. D. Kumar, R. Kapavarapu, M. V. B. Rao and M. Pal, *Tetrahedron Lett.*, 2013, **54**, 2989–2995; (c) S. Dhara, R. Singha, M. Ghosh, A. Ahmed, Y. Nuree, A. Das and J. K. Ray, *RSC Adv.*, 2014, **4**, 42604–42607; (d) S. Chaudhary, B. R. K. Shyamlal, L. Yadav, M. K. Tiwari and K. Kumar, *RSC Adv.*, 2018, **8**, 23152–23162.

32 (a) J. E. Baldwin, *J. Chem. Soc., Chem. Commun.*, 1976, 734–736, DOI: 10.1039/c39760000734; (b) C. D. Johnson, *Acc. Chem. Res.*, 2002, **26**, 476–482.

33 M. Jithunsa, M. Ueda and O. Miyata, *Org. Lett.*, 2011, **13**, 518–521.

34 A. R. Ali and L. Hu, *Asian J. Org. Chem.*, 2025, **14**, e202400421.

35 (a) J. Pospisil, C. Muller and A. Furstner, *Chem. – Eur. J.*, 2009, **15**, 5956–5968; (b) T. S. Mei, R. Giri, N. Maugel and J. Q. Yu, *Angew. Chem., Int. Ed.*, 2008, **47**, 5215–5219.

36 C. E. Castro, R. Havlin, V. K. Honwad, A. M. Malte and S. W. Moje, *J. Am. Chem. Soc.*, 2002, **91**, 6464–6470.

37 C. Niebel, V. Lokshin, M. Sigalov, P. Krief and V. Khodorkovsky, *Eur. J. Org. Chem.*, 2008, 3689–3699.

38 S. K. Gadakh and A. Sudalai, *RSC Adv.*, 2014, **4**, 57658–57661.

7490 | *Org. Biomol. Chem.*, 2025, **23**, 7483–7490

This journal is © The Royal Society of Chemistry 2025