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# Copper-Catalyzed Preparation of γ-Alkylidenebutenolides and Isocoumarins under Mild Palladium-Free Conditions

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**Abstract:** A general and efficient copper(I)-catalyzed cross-coupling and heterocyclization reaction of terminal alkynes and β-iodo-α,β-unsaturated acid derivatives has been developed under very mild conditions. This method provides easy access from good to excellent yields of a variety of 5-ylidenebutenolides and 3-substituted isocoumarins with excellent regio- and stereoselectivity. This procedure does not require the use of any expensive supplementary additives, and is palladium-free.

**Keywords:** alkynes; copper; cross-coupling; homogeneous catalysis; lactones

## Introduction

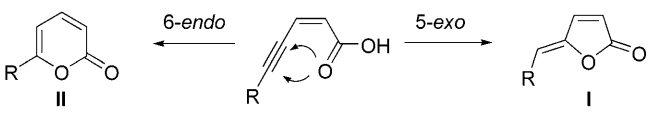
Butenolides and isocoumarins represent an important class of naturally occurring lactones with a wide range of biological and pharmacological uses such as antispasmodic, antifungal, herbicidal and pesticidal agents. Cytotoxic properties were also reported leading to a continued interest in the practical synthesis of this class of lactones, especially 5-ylidene-5*H*-furan-2-ones and 3-substituted isocoumarins.[1,2,3]

Transition metal-catalyzed cyclization of alkynes possessing a nucleophile in close proximity to the triple bond is one of the most important processes in organic synthesis, and affords the title compounds. Over the past decade a wide range of transition metal-based catalysts (Ag, Hg, Rh, Pd, Zn, Au, etc.) have been reported as effective catalysts to promote the intramolecular addition of carboxylic acids to alkynes.[4,5]

Indeed, the lactonization of 4-alkynoic acids was found to afford γ-alkylidenebutenolide **I** through a 5-*exo* pathway. In addition to the formation of **I**, six-membered lactones **II** have been obtained resulting from the 6-*endo* mode (Scheme 1).[6]

However, the synthesis often suffered from a lack of stereoselectivity. Similarly, it has been found that isocoumarins could be obtained under palladium catalysis conditions[7] or in the presence of zinc chloride.[8] It is worthy of note that one-pot procedures have also been reported and allow a direct access to γ-alkylidenebutenolides starting from the corresponding β-iodopropenoic and *ortho*-halobenzoic acids, respectively. However, these pathways all bring into play palladium-mediated reactions and Sonogashira coupling is the most widely used method.[9] A major drawback of this process in an industrial purpose is the use of two metal catalysts, making recovery of the expensive and toxic palladium catalyst difficult.

In the past few years there has been a resurgence of interest in copper(I)-catalyzed cross-coupling reactions.[10] Many synthetic protocols for the formation of




**Scheme 1.**

**Table 1.** Optimization studies for the Cu-catalyzed coupling heterocyclization sequence.

| Entry | Copper catalyst (%) | Base | Additive | Solvent | Time [h] | Temperature [°C] | Yield [%][a] |
|---|---|---|---|---|---|---|---|
| 1 | $Cu_2O$ (20%) | $K_2CO_3$ | – | DMF | 4 | 55 | 55 |
| 2 | CuCN (20%) | $K_2CO_3$ | – | DMF | 4 | 55 | 62 |
| 3 | CuCl (20%) | $K_2CO_3$ | – | DMF | 4 | 55 | 19 |
| 4 | CuBr (20%) | $K_2CO_3$ | – | DMF | 4 | 55 | 24 |
| 5 | CuI (20%) | $K_2CO_3$ | – | DMF | 4 | 55 | 80 |
| 6 | $CuBr_2$ (20%) | $K_2CO_3$ | – | DMF | 4 | 55 | 0 |
| 7 | CuI (20%) | $Cs_2CO_3$ | – | DMF | 4 | 55 | 9 |
| 8 | CuI (20%) | $K_3PO_4$ | – | DMF | 4 | 55 | 4 |
| 9 | CuI (20%) | $NaHCO_3$ | – | DMF | 4 | 55 | 55 |
| 10 | CuI (20%) | $Et_3N$ | – | DMF | 4 | 55 | 8 |
| 11 | CuI (20%) | none | – | DMF | 4 | 55 | 0 |
| 12 | CuI (20%) | none | – | DMF | 4 | r.t. | 0 |
| 13 | CuI (5%) | $K_2CO_3$ | – | DMF | 4 | 55 | 7 |
| 14 | CuI (10%) | $K_2CO_3$ | – | DMF | 4 | 55 | 23 |
| 15 | CuI (100%) | $K_2CO_3$ | – | DMF | 4 | 55 | 98 |
| 16 | CuI (20%) | $K_2CO_3$ | – | Toluene | 4 | 55 | 2 |
| 17 | CuI (20%) | $K_2CO_3$ | – | DMSO | 4 | 55 | 79 |
| 18 | CuI (20%) | $K_2CO_3$ | – | THF | 4 | 55 | 18 |
| 19 | CuI (20%) | $K_2CO_3$ | – | MeCN | 4 | 55 | 9 |
| 21 | CuI (20%) | $K_2CO_3$ | $Fe(acac)_3$ (60%) | MeCN | 6 | 55 | 73 |
| 22 | none | $K_2CO_3$ | $Fe(acac)_3$ (20%) | MeCN | 6 | 55 | $<5$ |
| 23 | CuI (2.5%) | $K_2CO_3$ | $Fe(acac)_3$ (7.5%) | MeCN | 6 | 55 | 71 |
| 24 | CuI (2.5%) | $K_2CO_3$ | $Fe(acac)_3$ (2.5%) | MeCN | 6 | 55 | 55 |

[a] Isolated yields.

carbon-carbon and carbon-heteroatom bonds based on copper(I) catalysts have been reported and they have been the subject of growing attention.[11,12,13] Recently, the use of copper salts has also been shown to mediate the synthesis of conjugated enynes.[14] In addition to being simple and mild, the newer copper-based methods accommodate substrates that are difficult to couple by palladium reactions.[14e,15] Copper catalysts have the further advantage of having low costs for use in large-scale industrial applications. The avoidance of expensive or air-sensitive ligands makes copper-based protocols very attractive from a synthetic point of view.

To the best of our knowledge, the one-pot palladium-free catalyzed synthesis of 5-ylidenebutenolides and isocoumarins from alkynes and β-iodopropenoic acid derivatives has never previously been reported. In all cases described in the literature, the synthesis of butenolides, pyran-2-ones, phthalides and isocoumarins starting from β-iodopropenoic acid derivatives and alkynes using copper as catalyst has been performed in two separate steps: (i) coupling of (*Z*)-3-iodopropenoic acid derivatives with terminal alkynes, typically by a Sonogashira-type reaction, and (ii) cyclization mediated by metal complexes,[16] bases,[17] and halogen.[18]

In addition, our interest in the field[19] has focused on an intramolecular addition of carboxylic acids to allenylstannanes for the construction of 3-substituted isocoumarins and α-pyrones.[20] We also described the synthesis of dienoic acids and enynes bearing a carboxylic acid function from β-iodovinylic acids and vinyltin or alkynylzinc reagents.[21] This methodology was then applied to the synthesis of 5-alkylidene-(arylidene)butenolides.[22]

On the basis of the above, we now report the first one-pot efficient and regioselective synthesis of 5-ylidene-5*H*-furan-2-ones and isocoumarins *via* the cross-coupling-heterocyclization reaction sequence of terminal alkynes and (*Z*)-3-iodopropenoic acid derivatives mediated by a simple salt. Herein we present a full account of our studies, including extensive investigations of the reaction scope.

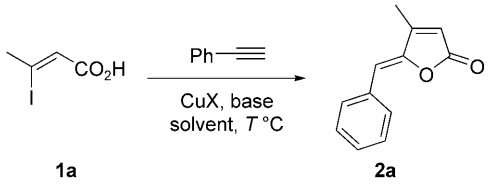
## Results and Discussion

As a starting point for the development of our transition metal-free methodology we chose to study the coupling of (*Z*)-3-iodobut-2-enoic acid with phenylacetylene. To optimize the reaction protocol, we examined a range of copper(I) salts, additives, solvents and bases (Table 1 and Scheme 2).

### Determination of the Best Catalytic System

In comparison with the corresponding palladium-catalyzed cross-coupling reactions, the copper-catalyzed version seemed to be less sensitive to the choice of




**Scheme 2.**

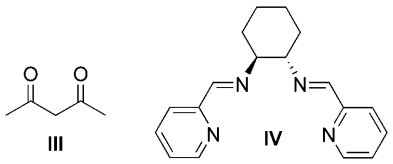



**Figure 1.**

the metal source. We examined the efficiency of copper(I) salts as catalyst for the tandem C–C coupling-heterocyclization reaction. We then studied the effects of different simple copper salts and the amount required for the coupling of (*Z*)-3-iodobut-2-enoic acid **1a** with phenylacetylene. All the copper (I) salts (CuI, CuBr, CuCl, $Cu_2O$, CuCN, etc.) tested and used with a base provided poor to good yields of the lactone **2a** (entries 1–5, Table 1). Upon optimization, we found that CuI was the most effective catalyst for the coupling of (*Z*)-3-iodobut-2-enoic acid **1a** with phenylacetylene (entry 5, Table 1). It should be noted that when copper(II) salts such as $CuBr_2$ were used as a catalyst instead of copper(I) salts, no reaction was observed (entry 6, Table 1).

The effects of the amount of copper required were investigated in the optimization process, and further experiments showed that the reaction was complete within 4 h in 80% yield using 20 mol% of CuI (entry 5, Table 1). Lowering the amount of catalyst to 5 or 10 mol%, provided unsatisfactory yields of the desired product (<30%) (entries 13 and 14, Table 1). Moreover, a stoichiometric amount of CuI improved the yield to 98% (entry 15, Table 1). At room temperature, no reaction occurred, and the starting material was completely recovered (entry 12, Table 1). Thereafter, different solvents were tested and we reached the conclusion that solvents with Lewis basicity properties were necessary. Indeed, the use of DMF or DMSO as a solvent could lead to the formation of good yields of heterocyclized product **2a** (entries 5 and 17, Table 1), whereas none of the desired products or unsatisfactory yields of the desired adducts were obtained in toluene, THF and $CH_3CN$ (entries 16, 18 and 19, Table 1). Our attention was next turned to the screening of different bases. Gratifyingly, potassium carbonate ($K_2CO_3$), an inexpensive base, was found to be highly effective and resulted in 80% yield of the coupled and cyclized product (entry 5, Table 1). On the other hand, $Cs_2CO_3$, $K_3PO_4$, $NaHCO_3$ and $Et_3N$, proved to give unsatisfactory yields (entries 7–10, Table 1). In addition, when the reaction was performed in the absence of base (entry 11, Table 1), the starting material was recovered unchanged. Lowering the amount of base to 1.5 equivalents resulted in poor yields and minor secondary by-products such as phenylacetylene dimer were detected (<10%). In order to decrease the amount of copper catalyst (less than 20%) we have evaluated the possibility to use a ligand on metal or to co-catalyze the reaction. Because 1,3-diketones **III**[23] or 2-pyridylimine **IV**[24] (Figure 1) were recently reported in Sonogashira or Ullmann-type reactions, we decided to test them in our transformation but no beneficial effects were observed.

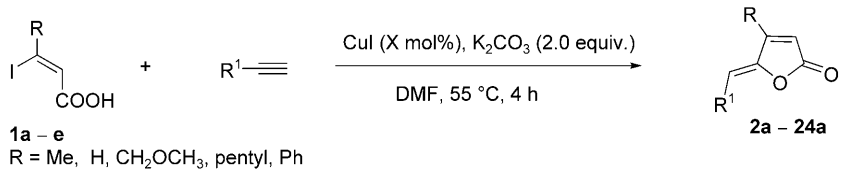
It should be noted that the reaction temperature was kept under 70 °C in order to preserve the temperature-sensitive arylidenebutenolides. More interestingly, we also examined the influence of an iron co-catalyst which was recently described by Taillefer et al. in the co-catalyzed arylation of nitrogen nucleophiles.[25] Using copper iodide and iron acetylacetonate in a 1/3 ratio, good yields were obtained while in the absence of copper salt, the reaction failed. Finally, using 2.5 mol% of copper iodide and 7.5 mol% of iron acetylacetonate, the lactone **2a** was obtained in 71% (entry 23, Table 1). With an equimolar amount of the two salts, we observed a slight decrease of yield (entry 24, Table 1). Comparison between the entries 1 and 23 (Table 1) clearly shows the beneficial effect of the co-catalytic system. Unfortunately, this observation was only valid for this particular alkyne and acid pair. Indeed, the reaction with octyne in place of phenylacetylene in the conditions of the entry 23, Table 1 failed to give the corresponding lactone. Identically, (*Z*)-3-iodopropenoic acid did not led to the 3-unsubstituted γ-alkylidenelactone. For these reasons and after a careful analysis of our results, the best set of reaction conditions has been established : 20 mol% of copper iodide (or CuI 1 equivalent in (*Z*)-3-iodoalkenoic acid case), 2.0 equivalents of potassium carbonate in DMF at 55 °C for 4 h.[26]

## Scope of the Method: Preparation of (*Z*)-5-Ylidenefuran-2(5*H*)-ones

To investigate the scope of the copper-catalyzed tandem coupling-heterocyclization reaction, a variety of commercially available terminal alkynes and (*Z*)-3-iodoacrylic acids was tested.[27]

The reaction described is extremely versatile and provides a convenient method for the synthesis of various 5-ylidene-5*H*-furan-2-ones with the (*Z*)-configuration exclusively, demonstrating that our strategy is very effective to prepare 5-ylidenebutenolides without




**Scheme 3.**

any trace of pyran-2-ones, giving a regio- and stereoselective character to the cyclization process (Scheme 3).

For example, alkynes bearing alkyl, alkenyl, aryl, heteroaryl, silyl and methoxy groups are tolerated (Table 2, entries 1–24). The presence of a long-chain alkyl group in the terminal alkyne did not affect the regioselectivity of the coupling-cyclization process (entries 13 and 14, Table 2), providing good yields of the corresponding butenolides **15a** and **16a** without formation of pyran-2-ones. However, in these cases, we found that the temperature ($<55\,^{\circ}C$) was a crucial parameter to obtain the expected butenolides as a single isomer. When the reaction temperature was in-

**Table 2.** Copper-catalyzed coupling-heterocylization reaction of β-iodopropenoic acid derivatives with terminal alkynes.

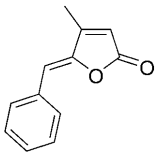
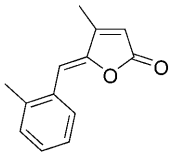
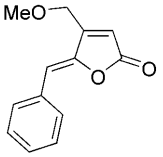
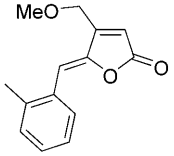
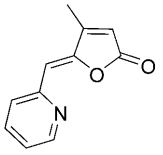
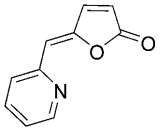
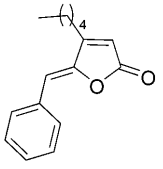
| Entry | R | $R^1$ | CuI [mol%] | Product | | Yield [%][a] |
|---|---|---|---|---|---|---|
| 1 | Me | Ph | 20 |  | **2a** | 80 |
| 2 | Me | *o*-Tol | 20 |  | **3a** | 82 |
| 3 | $CH_3OCH_2$ | Ph | 20 |  | **4a** | 86 |
| 4 | $CH_3OCH_2$ | *o*-Tol | 20 |  | **5a** | 84 |
| 5 | Me | 2-Pyridinyl | 20 |  | **6a** | 62 |
| 6 | H | 2-Pyridinyl | 20 |  | **7a** | 40 |
| 7 | *n*-Pent | Ph | 20 |  | **8a** | 75 |

**Table 2.** (Continued)

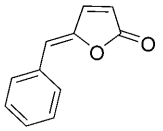
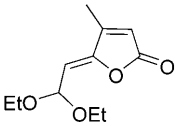
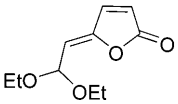
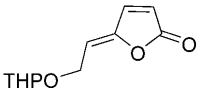
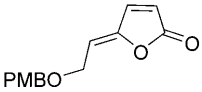
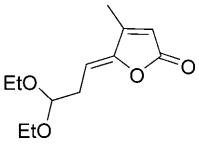
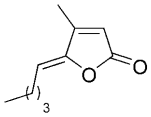
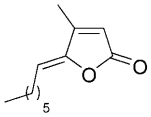
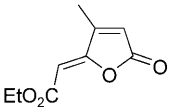
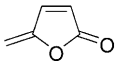
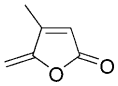
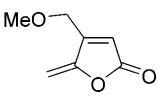
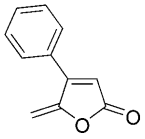
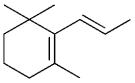
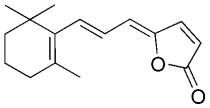
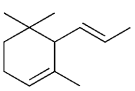
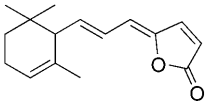
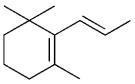
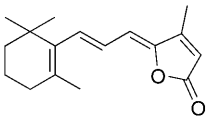
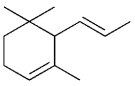
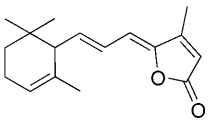
| Entry | R | $R^1$ | CuI [mol%] | Product | | Yield [%][a] |
|---|---|---|---|---|---|---|
| 8 | H | Ph | 100 |  | **9a** | 72 |
| 9 | Me | $CH(OEt)_2$ | 20 |  | **10a** | 85 |
| 10 | H | $CH(OEt)_2$ | 100 |  | **11a** | 65 |
| 11 | H | $CH_2OTHP$ | 100 |  | **12a** | 63 |
| 12 | H | $CH_2OPMB$ | 100 |  | **13a** | 52 |
| 13 | Me | $CH_2CH(OEt)_2$ | 100 |  | **14a** | 70 |
| 14 | Me | *n*-Bu | 100 |  | **15a** | 40 |
| 15 | Me | *n*-Hex | 100 |  | **16a** | 40 |
| 16 | Me | $CO_2Et$ | 100 |  | – | 0 |
| 17[b] | H | $SiMe_3$ | 100 |  | **17a** | < 5 |
| 18[b] | Me | $SiMe_3$ | 20 |  | **18a** | < 5 |
| 19[b] | $CH_3OCH_2$ | $SiMe_3$ | 20 |  | **19a** | < 5 |
| 20[b] | Ph | $SiMe_3$ | 20 |  | **20a** | < 5 |
| 21 | H |  | 20 |  | **21a** | 62 |
| 22 | H |  | 20 |  | **22a** | 63 |

**Table 2.** (Continued)

| Entry | R | $R^1$ | CuI [mol%] | Product | | Yield [%][a] |
|---|---|---|---|---|---|---|
| 23 | $CH_3$ |  | 20 |  | **23a** | 69 |
| 24 | $CH_3$ |  | 20 |  | **24a** | 66 |

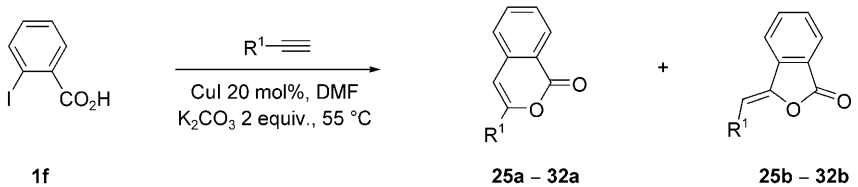
[a] Isolated yields.
[b] Compounds were only detected by GC/MS and were present in mixture with numerous by products.

creased to 65 °C, a mixture of butenolide and pyranone was obtained in a 1/1 ratio. The coupling-heterocyclization reaction of (*Z*)-**1a** with (7*E*)-1-(but-3-en-1-yn-4-yl)-2,6,6-trimethylcyclohex-1-ene (α)[28] (entries 21–23, Table 2) or (7*E*)-1-(but-3-en-1-yn-4-yl)-2,6,6-trimethylcyclohex-2-ene (β) (entries 22–24, Table 2) under the same conditions as described above provided reasonable yields of the desired trienylbutenolides **21a–24a**. A NOESY NMR experiment on **21a** confirmed the retention of the configuration of the double bonds of the starting materials, and a clean *Z* configuration of the exocyclic double bond of the butenolide is observed. No significant electronic effects were observed for an electron-donating substituent group at the *ortho*-position of the terminal aromatic ring (entries 2 and 4, Table 2). In contrast, the introduction of an electron-withdrawing group at the *ortho*-position of the terminal aromatic ring markedly diminished the yield of the coupling-heterocyclization sequence, presumably due to the reduced electron density on the triple bond (entry 8, Table 2). In another case, trimethylsilylacetylene afforded with a very low conversion rate the very sensitive five-membered ring product exclusively, in which a desilylation reaction certainly occurs in these experimental conditions (entries 17–20, Table 2). Attempts to improve the yield by increasing the amount of copper catalyst were unsuccessful.

## Scope of the Method: Preparation of Isocoumarins

With the reaction conditions thus optimized, and in order to explore the generalization of our method, attention was next directed toward the synthesis of new heterocycles from *o*-iodobenzoic acids and terminal alkynes by using the same strategy. Indeed, compound **1f** underwent the domino sequence to provide reaction mixtures in which 3-substituted isocoumarins **25a–32a** were the major products and (*Z*)-5-ylidene phthalides **25b–32b** the minor ones (Scheme 4). However, in the cases of phenylacetylene and 3,3-diethoxypropyne, mixtures of the five- and six-membered rings were respectively obtained in 50/50 and 95/5 ratios (entries 1 and 3, Table 3) (combined yield = 45%). These heterocyclic compounds have previously been prepared by the palladium-catalyzed coupling of 2-halobenzoate esters or 2-halobenzonitriles with alkenes,[29] vinylic stannanes[30] or terminal alkynes,[9a,31] with subsequent cyclization or π-allylnickel cross-coupling and palladium-catalyzed cyclization,[32] or by palladium-catalyzed annulation of terminal alkynes and 2-iodophenols.[33] Isocoumarins have also been prepared by the palladium-catalyzed annulation of internal alkynes.[34] The cross-coupling of *o*-iodobenzoic acid and terminal alkynes produces either unsaturated phthalides[35,36] or 3-substituted isocoumarins as major products.[7,37]

For the coupling-intramolecular cyclization sequence, "5-*exo-dig*" or "6-*endo-dig*" closure is allowed according to Baldwin's rules.[38] However, the reasons for the regioselectivity observed associated

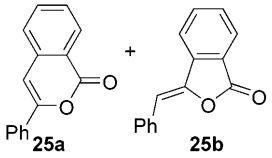
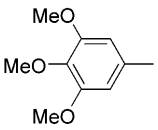
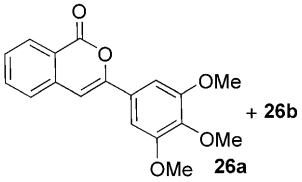
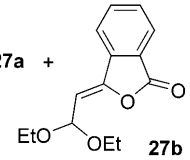
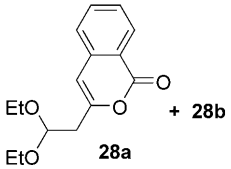
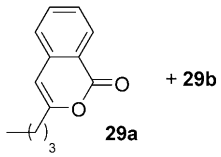
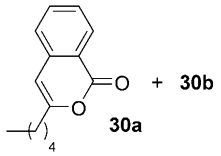
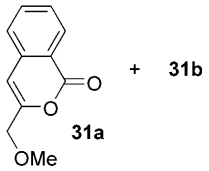
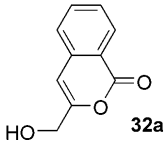



**1f** **25a – 32a** **25b – 32b**

**Scheme 4.**

**Table 3.** Copper-catalyzed reaction of *ortho*-iodobenzoic acid with alkynes.

| Entry | $R^1$ | Product | **a/b** | Yield [%][a] |
|---|---|---|---|---|
| 1 | Ph |  **25a** + **25b** | 50/50 | 45 |
| 2 |  |  + **26b** **26a** | 55/45 | 54 |
| 3 | $(EtO)_2CH$ | **27a** +  **27b** | 5/95 | 70 |
| 4 | $(EtO)_2CHCH_2$ |  + **28b** **28a** | 65/35 | 64 |
| 5 | *n*-Bu |  + **29b** **29a** | 70/30 | 65 |
| 6 | *n*-Pent |  + **30b** **30a** | 72/28 | 58 |
| 7 | $CH_3OCH_2$ |  + **31b** **31a** | 75/25 | 43 |
| 8 | $HOCH_2$ |  **32a** | 100/0 | 24 |

[a] Isolated yields of isocoumarins.

with the use of CuI (20 mol%) as catalyst system are not yet clear at this stage. Despite their well-known role in the formation of phthalides, Cu(I) salts are also known to catalyze the intramolecular cyclization of 2-(1-alkynyl)benzoic acid or its derivative to the six-membered lactone ring.[12e,39] In our case, the reaction of 2-iodobenzoic acids and terminal alkynes under regio- and stereocontrol gave reasonable yields of mixtures of the six- and five-membered ring resulting from the 6-*endo-dig* and 5-*exo-dig* cyclization mode. Surprisingly, the alkyne bearing propargyl acetal or alcohol functions resulted from an opposite cyclization mode (entries 3 and 8, Table 3). In the case of a terminal alkyne substituted with a long-chain alkyl group, a six-membered heterocycle was also formed as major product with moderate isolated yield (entries 5 and 6, Table 3). It should be noted that 3-pentylisocoumarin **30a** is a precursor for a nat-

urally occurring isocoumarin (artemidin) and therefore a compound of biological interest.[40] In another case an alkyne bearing a methoxy group furnished a mixture of six-membered ring product **31a** and five-membered ring **31b** in a 75:25 ratio. For the coupling of iodobenzoic acid with phenylacetylene, a mixture of isocoumarin and phthalide was formed in similar proportions with 45% yield. When 2-iodo-5-nitrobenzoic acid was reacted with phenylacetylene under the conditions given, only trace amounts of the isocoumarin could be obtained. This result indicates that the electron-withdrawing groups on the aromatic ring must play an important role in the reaction. Attempts to improve the yield by increasing the amount of copper catalyst met with no success.

As shown in Table 2 and Table 3, better yields were obtained with (*Z*)-3-iodoalkenoic acids **1a–e** than with 2-iodobenzoic acid **1f**. Extension of this coupling-heterocyclization sequence using copper catalyst to other classes of functionalized β-iodopropenoic acid derivatives is currently being studied in our laboratory.

## Conclusions

The aim of this research was to develop an efficient and cheaper method for the synthesis of a (*Z*)-5-ylidene-5*H*-furan-2-one library under mild and more environmentally friendly conditions. These issues were addressed by replacing the expensive palladium catalysts with less expensive 20 mol% CuI. In summary, we have developed a practical and general catalytic system [Cu(I) salts in DMF] for the efficient tandem coupling-heterocyclization reaction of (*Z*)-3-iodopropenoic acid derivatives with terminal alkynes, leading to the easy formation of an important range of (*Z*)-5-alkylidene- or arylidene-5*H*-furan-2-ones that can also be extended to the preparation of 3-substituted isocoumarins. Compared to other copper-catalyzed Sonogashira-type reactions, we found that the reaction temperature is significantly lower (90–140 °C *vs.* 50 °C) indicating a strong effect of the close carboxylate function. As a possible explanation we thought that the oxidative addition step of copper into the carbon/iodine bond would be favored through an intramolecular process from a copper carboxylate. In order to confirm this point, we have realized experiments with (*E*)-3-iodopropenoic acid under the same experimental conditions which were unsuccessful in leading to the corresponding enynoic acids. Finally, the present methodology does not involve the use of an expensive, air-sensitive palladium(0) catalyst or any additive ligand. Further applications of this catalytic system to generate butenolide- and isocoumarin-based chemical libraries of potential pharmacological interest are under investigation in our laboratory.

## Experimental Section

All reactions were carried out under inert atmosphere (Ar or $N_2$). DMF was dried by distillation over $CaH_2$. The petroleum ether (PE) used was the fraction boiling in the range 40–60 °C. Flash chromatography was carried out with Merck silica gel (silica gel, 230–400 mesh). $^1$H NMR spectra were recorded at 200 or 300 MHz using $CDCl_3$ as solvent. Findings, reported using the residual solvent proton resonance of $CDCl_3$ ($\delta_H = 7.25$ ppm) as internal reference, were as follows (in order): chemical shift ($\delta$ in ppm in relation to $Me_4Si$), multiplicity (s, d, t, q, m, b for singlet, doublet, triplet, quartet, multiplet, broad) and coupling constants (*J* in Hz). $^{13}$C NMR sopectra were recorded at 50.3 MHz using the $CDCl_3$ solvent peak at $\delta_C = 77.0$ ppm as reference. Mass spectra were recorded on a Applied Biosystems QSTAR Elite spectrometer. Melting points were uncorrected.

### General Procedure for the Synthesis of γ-Alkylidenebutenolides

A dry Schlenk tube equipped with a Teflon-coated magnetic stirrer was charged with $K_2CO_3$ (2.8 g, 20.0 mmol, 2 equiv.) and (*Z*)-3-iodobut-2-enoic acid (2.1 g, 10.0 mmol, 1 equiv.). The mixture vessel was evacuated and backfilled with argon. Anhydrous DMF (40 mL) was added and the suspension was stirred for 15 min. Then, the mixture was degassed at −80 °C for 10 min and backfilled with argon. After reaching room temperature, the alkyne (20.2 mmol, 2 equiv.) was added and finally CuI (0.384 g, 2.02 mmol, 20 mol%). The Schlenk tube was sealed and then placed in a preheated oil bath at 65 °C and the mixture stirred overnight. The reaction mixture was allowed to reach room temperature and was partitioned between diethyl ether (40 mL × 3) and saturated aqueous $NH_4Cl$ (30 mL). The organic portions were dried over $Na_2SO_4$, filtered and concentrated by rotary evaporation. The material thus obtained was purified by flash chromatography on silica gel to give the desired γ-alkylidenebutenolide.

**(*Z*)-5-Benzylidene-4-methylfuran-2(5*H*)-one (2a):** FT-IR (KBr): $\nu = 2987$, 1773, 1754, 1645, 1596, 1442, 1386 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 200 MHz): $\delta = 7.83$–7.14 (5H, m), 6.49 (1H, s), 6.04 (1H, s), 2.20 (3H, s); $^{13}$C NMR ($CDCl_3$, 50 MHz): $\delta = 22.2$, 104.6, 112.3, 126.2, 127.8, 129.4, 132.0, 156.7, 161.5, 168.6; MS (EI): *m/z* (%) = 186 ($M^+$, 100), 158 (25), 157 (17), 130 (23), 129 (42), 128 (10), 118 (22), 115 (32), 90 (46), 89 (39), 64 (13), 63 (24), 51 (14), 40 (17), 39 (42); HR-MS (EI): *m/z* = 187.0688, calcd. for $C_{12}H_{10}O_2$ ($M^+$): 187.0681.

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