ChemPubSoc Europe

DOI: 10.1002/ejoc.201901099

EurJOC European Journal of Organic Chemistry

Full Paper

Intramolecular Oxacyclization

Tandem One-Pot Approach to *N*-Substituted Lactones by Carbon–Carbon Coupling Followed by 5-*exo*-dig or 6-*endo*-dig Cyclization: DFT Studies and Cyclization Mode

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Abstract: A one-pot approach has been developed for the preparation of a five or six-membered ring of unsaturated lactones bearing an amino group through a tandem coupling oxacyclization reaction. This tandem process involves Sonogashira-like cross-coupling followed by 5-*exo*-dig or 6-*endo*-dig intramolecular oxacyclization, according to the nature of the alkynes substituent. Furthermore, DFT calculations were performed to analyze the origin of this regioselectivity of cyclization.

Introduction

Five or six-membered lactones (butenolides, pyrones) bearing a nitrogen-containing unit are important heterocyclic ring systems, which can be present in several natural products and have a diverse range of biological properties. As shown in Figure 1, the natural compound Basidalin **A** is a novel butenolide bearing an amino group at position 4, which seems to have good antitumor activity against leukemia.[1] The Uncinine **B**, which is based on a combination of the pyrrolidinone and γ-alkylidenebutenolide fragments, exhibits cytotoxicity against the Hep G2 cell line (IC50 6.1 μg/mL).[2] The synthetic γ-alkylidenebutenolide **C** displays an antibacterial activity with a minimum inhibitory concentration (MIC) value of 20 μg/mL against *Escherichia coli* while γ-alkylidenebutenolide **D** exhibits cytotoxic activity against Ec9706 cells.[3] In addition, the α-pyranone carboxamide **E** is reported as promising anti-hepatitis C agent.[4] These skeletal motifs also feature as intermediates for the synthesis of related heterocycles and complex natural products.[5]

In the light of their biological properties, different approaches have been then developed to synthesize these heterocycles.[6] Among them, the widely used approach is based on an intramolecular cyclization between carboxylic acid and alkyne functions, promoted by metal-catalyst, (Ag, Hg, Rh, Pd, Cu, ...).[7] Such method can afford both five-membered lactones through a 5-*exo* process and/or six-membered lactones resulting from a 6-*endo* process.[8] In the last decade, our group has developed a selective approach for the preparation of such lactones via a tandem coupling/cyclization reaction between β-(di)halogeno-α,β-unsaturated acids and terminal alkynes in the presence of catalytic amount of copper(I) catalyst (Scheme 1).[9] During this work, we reported that the regioselectivity of the cyclization was exclusively in favor of the 5-membered-ring lactone. This methodology was therefore extended to the preparation of natural compounds such as Nostoclides.[10] To further explore the synthetic potential of β-iodo-α,β-unsaturated carboxylic acid, we report herein an extension of our methodology for the regioselective preparation of γ-alkylidenebutenolides and pyranones bearing an amino group. Finally, DFT calculations have been carried out to support experimental data high-

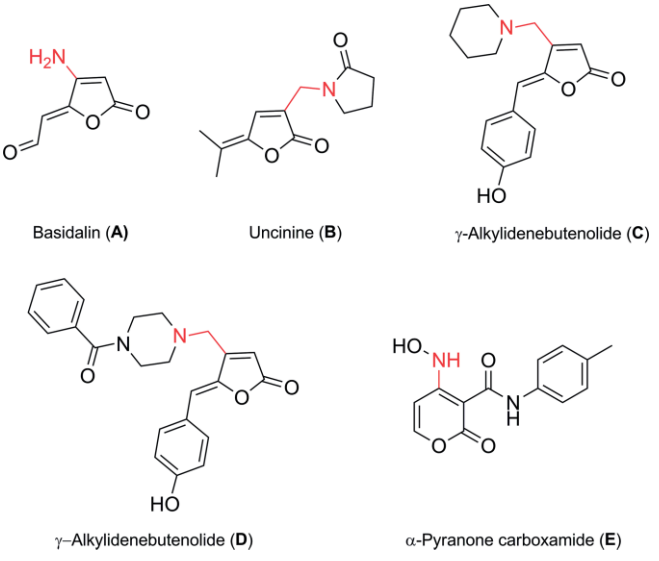

Figure 1. γ-Alkylidenebutenolides and α-pyranone bearing an amino group with biological properties.

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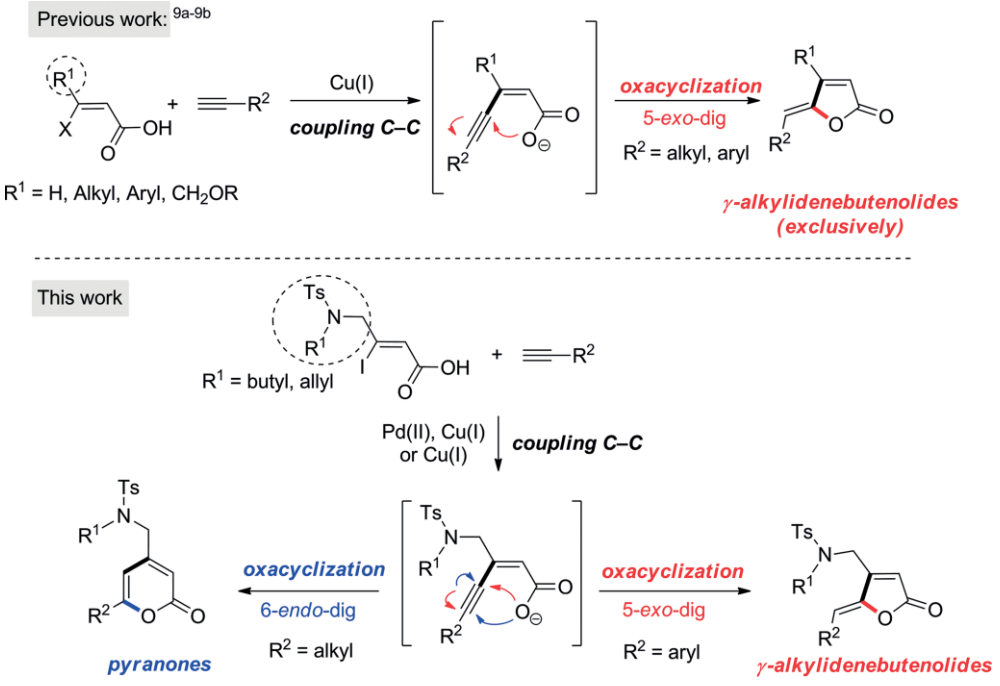


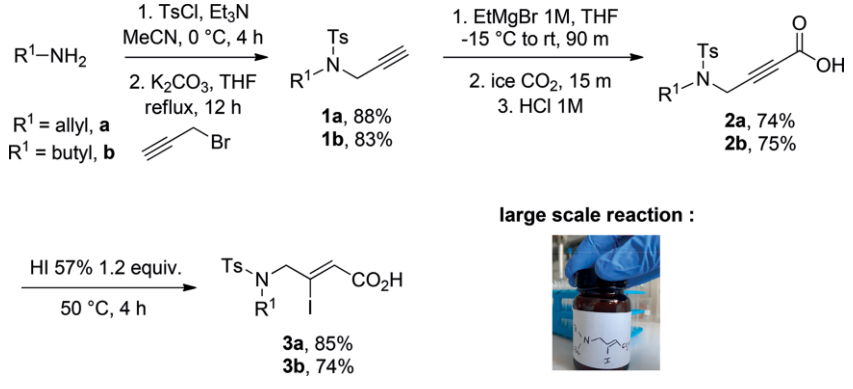
Scheme 1. Tandem Sonogashira coupling/oxacyclization.

lighting the impact of the nature of the alkyne on the regioselectivity.

Results and Discussion

Firstly, we turned our attention to the preparation of β-iodo-α,β-unsaturated carboxylic acid bearing an amino group according to the sequence illustrated in Scheme 2. The synthesis started with the tosylation of commercial allyl and butylamine as reported in the literature,[11] followed by the propargylation using propargyl bromide in the presence of K_2CO_3 as a base in THF, afforded **1a** and **1b** with good yields.[12] Then, we prepared the alkynoic acid **2a** and **2b** by carbonatation with EtMgBr/$CO_{2(ice)}$. The resulting acids reacted with hydroiodic acid, using conditions previously reported to obtain the corresponding (*Z*)-3-iodovinylic acids **3a** and **3b** with good yields as single isomers.[13] Furthermore, by following this procedure, each acid was obtained on a multigram scale.

3a and *p*-methoxyphenylacetylene were selected as the reference system to perform the optimized catalytic system for the tandem coupling/5-*exo*-dig cyclization reaction (Table 1). In the first approach, the reaction was performed with the catalytic system previously discovered by our group.[9] Only the starting materials were recovered after 12 h in such conditions (Table 1, entry 1), even using different solvents, such as MeCN, THF, and DMSO, (Table 1, entries 2–4). An increase of the temperature from 55 °C to 100 °C led to β-elimination adducts (Table 1, entry 5). Some traces of **4d** were observed with a stoichiometric amount of catalyst at 55 °C (Table 1, entry 6). Pleasingly, the use of 1.2 equiv. of CuI led to the desired product with 70 % yield (Table 1, entry 7). These data clearly indicate that an excess of copper is required for this reaction. This result could be explained by the presence of nitrogen atoms in the starting material, such as the β-iodo-α,β-unsaturated carboxylic acids **3a–b**, which is able to complex the copper(I) catalyst and prevent it reaching the reaction site.[14] Next, we focused on the



Scheme 2. Preparation of β-iodo-α,β-unsaturated carboxylic acids **3a** and **3b**.

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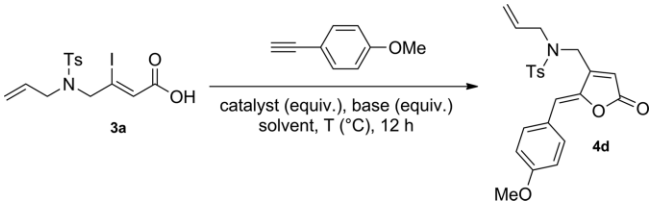
use of the palladium catalyst system for the tandem coupling/cyclization process (Table 1, entries 8–12). We explored different palladium sources in combination with CuI (Table 1, entries 8–12), the best Pd salt was found to be $Pd(PPh_3)_2Cl_2$ rather than $Pd(PPh_3)_4$ or $Pd(OAc)_2$. Further optimization revealed that the catalyst loading could be reduced to 5 mol-% under the same condition to obtain **4d** in 70 % yields (Table 1, entry 11). A decrease of the yields to traces was observed by decreasing the temperature from 55 °C down to 25 °C (Table 1, entry 12) under the same conditions.

Table 1. Optimization of γ-alkylidenebutenolide preparation.[a]



Entry	Base [equiv.]	Solvent	Catalyst [equiv.]	T [°C]	Yield [%][b]
1	K_2CO_3 (2)	DMF	CuI (0.2)	55	0[c]
2	K_2CO_3 (2)	THF	CuI (0.2)	55	0[c]
3	K_2CO_3 (2)	DMSO	CuI (0.2)	55	0[c]
4	K_2CO_3 (2)	MeCN	CuI (0.2)	55	0[c]
5	K_2CO_3 (2)	DMF	CuI (0.2)	100	0[d]
6	K_2CO_3 (2)	DMF	CuI (1)	55	10
7	K_2CO_3 (2)	DMF	CuI (1.2)	55	70
8	Et_3N (3)	DMF	$Pd(PPh_3)_4$ (0.1) + CuI (0.2)	55	54
9	Et_3N (3)	DMF	$Pd(OAc)_2$ (0.1), + PPh_3 (0.2) + CuI (0.2)	55	60
10	Et_3N (3)	DMF	$PdCl_2(PPh_3)_2$ (0.1) + CuI (0.2)	55	72
11	Et_3N (3)	DMF	$PdCl_2(PPh_3)_2$ (0.05) + CuI (0.2)	55	70
12	Et_3N (3)	DMF	$PdCl_2(PPh_3)_2$ (0.1) + CuI (0.2)	25	trace

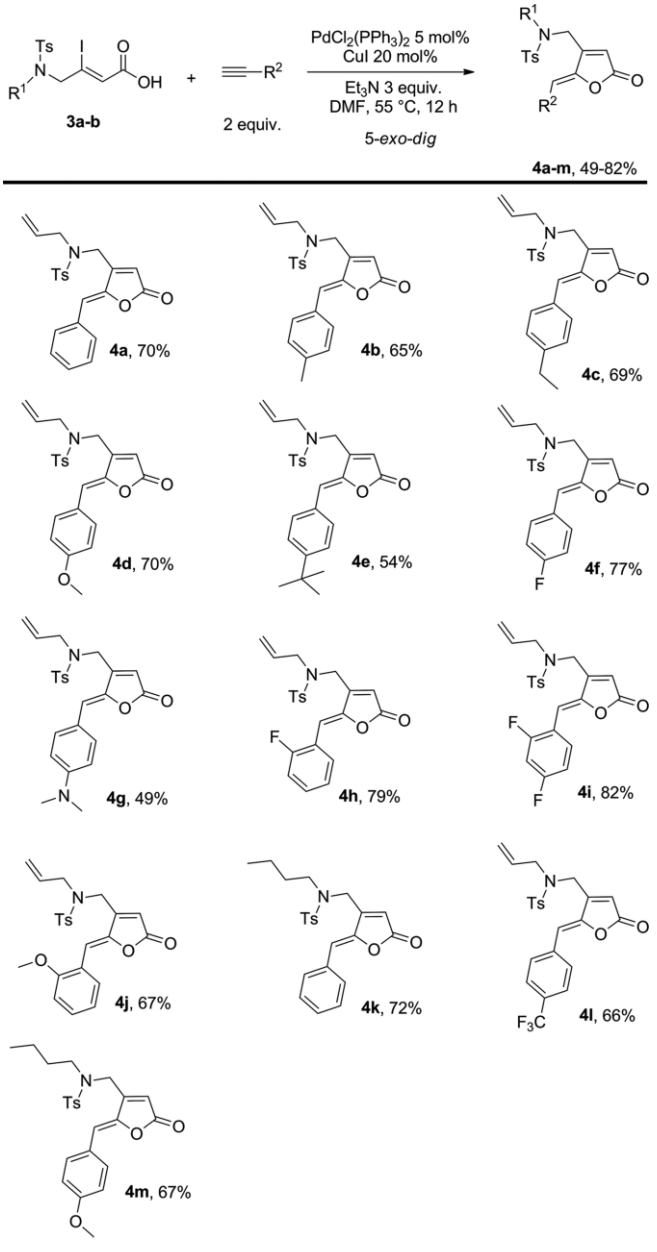
[a] Reaction conditions: Substrate **3a** (0.70 mmol), 4-methoxyphenylacetylene (2 equiv.) in 20 mL of solvent. [b] Isolated yield after column chromatography. [c] Starting material **3a**. [d] Alkynoic acid **2a**.

Finally, the reaction was performed using 10 mol-% $Pd(PPh_3)_2Cl_2$ with 20 mol-% CuI, in combination with Et_3N (3 equiv.) at 55 °C. In such conditions, **4d** was obtained with a good yield of 72 % (Table 1, entry 10).

We then focused on the scope and limitations of this coupling/5-*exo*-dig oxacyclization process with various arylic alkynes by using the optimal reaction conditions (i.e. 5 mol-% $Pd(PPh_3)_2Cl_2$ with 20 mol-% CuI, in combination with Et_3N (3 equiv.) at 55 °C). As shown in Scheme 3, the reaction afforded the corresponding *N*-substituted butenolides **4a–m** with moderate to excellent yields (49–82 %).

The regioselectivity and the stereochemistry of the double bond were unambiguously confirmed thanks to a single-crystal X-ray diffraction study of compound **4j** (Figure 2, for details see ESI).[15] The suitable single-crystal of **4j** for X-ray diffraction was obtained by crystallization from CH_2Cl_2.

Interestingly, a mixture of **4d** with the corresponding pyranone was obtained in a 1:1 ratio when the reaction was performed at 75 °C (see ESI). A further increase of the temperature from 75 °C to 100 °C did however not improve this ratio in favor of the pyranone. At this stage, we assumed that a temperature below 55 °C is essential in order to obtain the expected *N*-substituted butenolides as single isomers.



Scheme 3. Substrate scope in Pd-catalyzed *N*-substituted γ-alkylidenebutenolide synthesis.

In contrast to aryl-substituted alkynes, the presence of linear aliphatic or cyclohexyl-substituted alkynes affects the regioselectivity of the tandem process. On the one hand, at 55 °C we obtained a mixture of 5-*exo*-dig and 6-*endo*-dig cyclization at an average ratio of 75:25 in favor of 6-*endo*-dig cyclization. On the other hand, reactions performed at 35 °C with the same alkyne afforded only the 6-*endo*-dig cyclization product (Scheme 4).

The results of this study show that the regiochemistry of intramolecular cyclization is greatly influenced by the nature of the alkyne substituent. In short, the aryl-substituted alkynes undergo only 5-*exo*-dig cyclization to give *N*-substituted γ-alkylidenebutenolides products, while linear aliphatic or cyclohexyl-substituted alkynes give only 6-*endo*-dig cyclization and *N*-sub-

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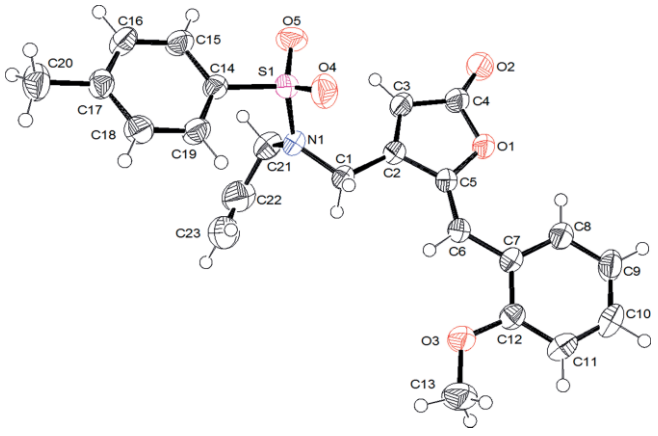
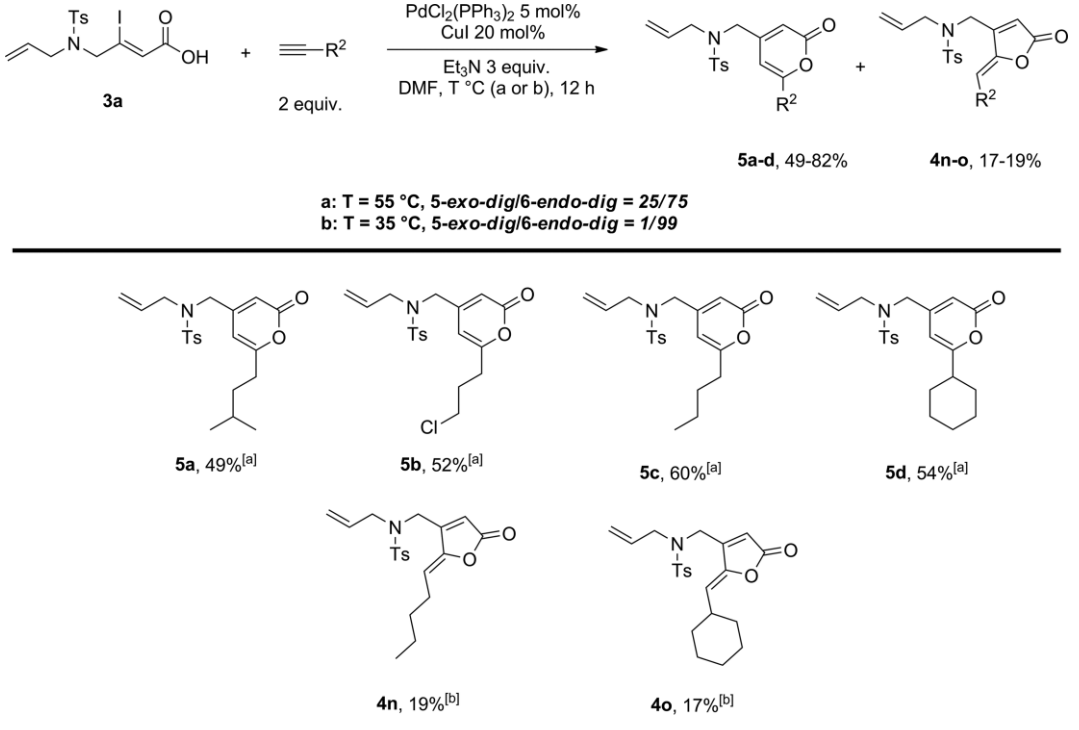


Figure 2. X-ray single-crystal structure of **4j** (thermal ellipsoids are draw at 50 % probability level).

stituted pyranones products. These results are in contrast to our previous work, in which we highlighted that the structure of the starting substrate affects the regioselectivity of the cyclization.[16a] Briefly, previously we demonstrated that 5-*exo*-dig was mainly obtained with non-aromatic systems, while 6-*endo*-dig was promoted in the case of heteroaromatic derivatives, and a mixture of coumarin and phthalide was obtained when aromatic systems were used.[16b]

A plausible mechanism for this present tandem coupling/cyclization was postulated (Scheme 5) in accordance with the work of Burton et al.[17] Initially, we propose the formation of carboxylate **A** followed by the oxidative insertion of the Pd(0) in the carbon iodide bond, creating a Pd(II) intermediate **B**. This intermediate could be further transformed into the cyclization product by the catalysis of Pd(II) through the σ-vinyl-palladium intermediate obtained by oxacyclization. The protodemetalation with Et_3NH^+ of σ-vinyl-palladium intermediate could afford the expected lactone and the $Pd(0)L_2$ released in the Sonogashira cross-coupling.

We also focused our attention to understanding the role of the nature of alkyne in promoting the different cyclization modes. Considering L = PMe_3,[18] R^2 = Ph and Cy respectively as aromatic and aliphatic model, the relative formation energies of intermediates $\mathbf{I_1}$, $\mathbf{I_2}$, $\mathbf{I_3}$, $\mathbf{I_4}$, $\mathbf{I_5}$, $\mathbf{I_6}$ and products **4** and **5** were determined *in-silico*. Briefly, DFT calculations were performed in DMF with a convergence criterion of 10^{-6} Hartree using Turbomole 7.0 program package along with DFT/B3LYP/def-TZVP level of theory calculations combining the COSMO-RS model and the resolution of identity (RI) approximation. Cartesian coordinates of investigated species are tabulated in SI2 along with those determined for intermediate $\mathbf{I_1}$, reactants and products as a function of R^2 structure. Each ΔG (kcal mol^{-1}) value, reported in Scheme 5, corresponds to the Gibbs free energy of the corresponding reaction step. Except for the products, all ΔG values are positives with highest values for the protodemetalation reactions which seem to the rate-determining step of the entire transformation. However, by considering the Δ(ΔG) differences between $\mathbf{I_3}$-Ph/$\mathbf{I_4}$-Ph (Δ(ΔG) = −2.4 kcal mol^{-1}) and $\mathbf{I_3}$-Cy/$\mathbf{I_4}$-Cy (Δ(ΔG) = +1.3 kcal mol^{-1}), $\mathbf{I_5}$-Ph/$\mathbf{I_6}$-Ph (Δ(ΔG) = −2.6 kcal mol^{-1}) and $\mathbf{I_5}$-Cy/$\mathbf{I_6}$-Cy (Δ(ΔG) = +0.5 kcal mol^{-1}), one can appreciate that DFT results unambiguously corroborate the influence of the nature of R^2 on the cyclization mode during



Scheme 4. Substrate scope in Pd-catalyzed *N*-substituted pyranones synthesis.

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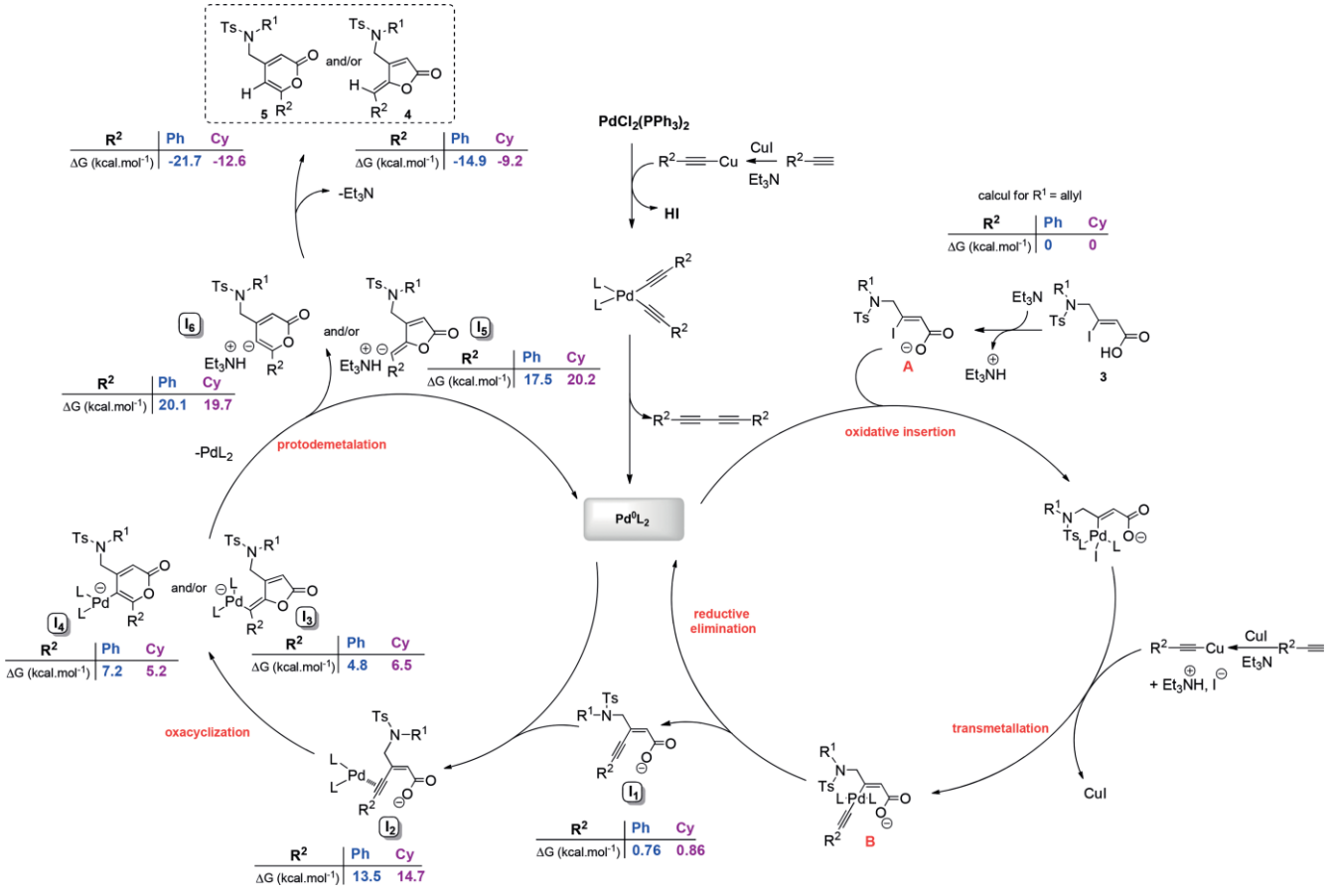

Scheme 5. Proposed mechanism for the tandem coupling/cyclization reaction along with energy profiles of intermediates I_1–I_6 and products with respect to respective reactants (where ΔG, kcal mol^{-1}, during the DFT calculations, done in the case of R^2 = Ph or Cy, L = PMe_3).

the oxacyclization step. Furthermore, this tendency was also confirmed by the natural population analysis of carbons in the alkyne group (Figure 3), showing that the local charge on the carbon atom leading the 5-*exo*-dig reaction (denoted β in Figure 3) is positive on contrary of the other (denoted α in Figure 3). This result agrees with observations made by Wang and Burton,[17] and by Uchiyama et al. in basic conditions.[19] However, lower differences between the charges of these two carbons are observed in the case of the linear aliphatic or cyclohexyl-substituted alkynes, which may also explain why the 6-*endo*-dig product is mainly obtained in this case, in contrary of aryl-substituted alkynes. In the case of the linear aliphatic or cyclohexyl-substituted alkynes, the temperature dependence in the production of 5-*exo*-dig observed experimentally to increase with the temperature (Scheme 4), could be related to the relatively low differences, in comparison with aryl-substituted alkynes, between charges on these carbons and also by between the formation energies observed in the case of the intermediates **I_3** and **I_4** in the case of R^2 = Cy.

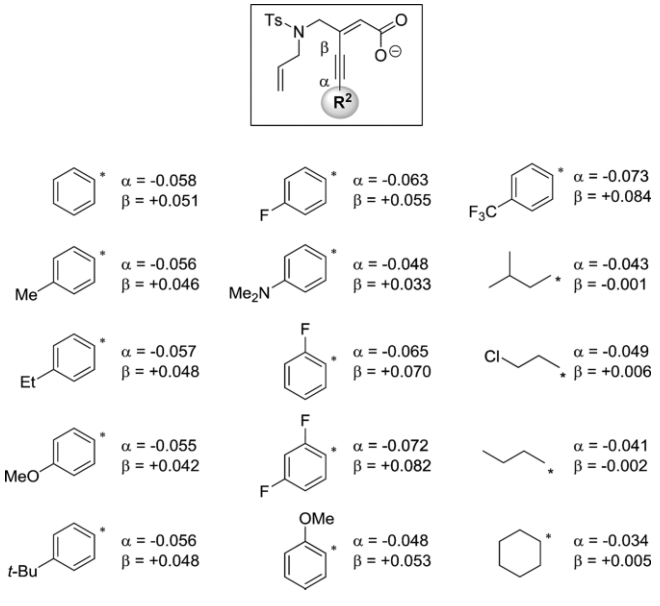

Figure 3. Natural population analysis as a function of the nature of the alkyne substituent.

Conclusions

In summary, we have developed a useful method for the synthesis of β-iodo-α,β-unsaturated carboxylic acid bearing an amino group in four steps from readily available primary amine. We have then demonstrated that the resulting (*Z*)-4-(*N*-alkyl)-3-iodobut-2-enoic acids afforded a novel series of *N*-substituted pyranones and *N*-substituted γ-alkylidenebutenolides, prepared

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using a tandem coupling/cyclization reaction. We have also studied the regiochemistry of this reaction as a function of the nature of the alkynes substituent and temperature prior proposing a mechanism for this tandem coupling/cyclization reaction. A relationship between substituted alkynes and product was then examined along with DFT calculations.

Experimental Section

General procedure for the synthesis of carboxylic acids 2a–b:

In a round-bottomed flask, *N*-propargylamine **1a–b** (0.05 mol, 1 equiv.) was dissolved in THF (20 mL). A solution of EtMgBr 1 M in Et_2O (60 mL, 0.6 mol) was slowly added at –15 °C. The mixture was then stirred for 90 min at room temperature. Solid carbon dioxide was added at 0 °C and the solution was vigorously stirred at room temperature. After 15 min, the mixture was cooled to 0 °C and acidified with HCl 1 M to obtain pH = 1. The resulting precipitate was filtered and washed with hexane.

4-(*N*-Allyl-4-methylphenylsulfonamido)but-2-ynoic acid (2a): Following the general procedure, **2a** was prepared from *N*-propargylamine **1a**; **2a** was isolated as a yellow solid (10.88 g, 74 % yield). M.p. 104–106 °C; IR (ATR) ν_{max} = 2971, 2917, 2243, 1683, 1622, 1598, 1411, 1341, 1283, 1208, 1157, 890, 748, 660, 543 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.73 (d, *J* = 8.2 Hz, 2H), 7.32 (d, *J* = 8.2 Hz, 2H), 5.58 (ddt, *J* = 17.0, 9.9, 6.8 Hz, 1H), 5.33–5.25 (m, 2H), 4.22 (s, 2H), 3.82 (d, *J* = 6.8 Hz, 2H), 2.42 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 156.3, 144.4, 135.1, 131.4, 129.9, 127.7, 120.8, 83.0, 49.7, 35.9, 21.6; HRMS (ESI): *m/z calcd.* for $C_{14}H_{16}NO_4S$ $[M + H]^+$: 294.07946, found 294.07905.

4-(*N*-Butyl-4-methylphenylsulfonamido)but-2-ynoic acid (2b): Following the general procedure, **2b** was prepared from *N*-propargylamine **1b**; **2b** was isolated as a white solid (11.62 g, 75 % yield). M.p. 98–100 °C; IR (ATR) ν_{max} = 3355, 3262, 2969, 2659, 1732, 1706, 1599, 1414, 1330, 1244, 1159, 1094, 912, 815, 766, 661, 548 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) = 8.89 (s, 1H),7.71 (d, *J* = 8.2 Hz, 2H), 7.30 (d, *J* = 8.2 Hz, 2H), 4.25 (s, 2H),3.17 (t, *J* = 7.3 Hz, 2H), 2.40 (s, 3H), 1.53 (quint, *J* = 7.3 Hz, 2H), 1.35 (sext, *J* = 7.3 Hz, 2H), 0.92 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 155.5, 144.1, 135.0, 129.8, 127.5, 82.5, 76.6, 46.6, 36.2, 29.4, 21.4, 19.6, 13.5; HRMS (ESI): *m/z calcd.* for $C_{14}H_{20}NO_4S$ $[M + H]^+$: 310.11130, found 310.11092.

General Procedure for the preparation of iodobut-2-enoic acids 3a–b:

In a two-necked round-bottomed flask, carboxylic acid **2a–b** (0.01 mol, 1 equiv.) was dissolved in 15 mL of Et_2O. HI 57 % (1.6 mL, 0.012 mol) was added dropwise, and the mixture was stirred at 50 °C for 4 h. Then, a 20 % solution of $Na_2S_2O_3$ (10 mL) was added and the mixture was then stirred for 30 min. The mixture was rapidly extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with brine (2 × 10 mL), dried with anhydrous $MgSO_4$ and concentrated under vacuum. The crude solid was recrystallized from CH_2Cl_2.

(*Z*)-4-(*N*-Allyl-4-methylphenylsulfonamido)-3-iodobut-2-enoic acid (3a): Following the general procedure, **3a** was prepared from carboxylic acid **2a**; **3a** was isolated as a white solid (3.60 g, 85 % yield). M.p. 110–112 °C; IR (ATR) ν_{max} = 2905, 1696, 1622, 1598, 1410, 1340, 1283, 1207, 1156, 907, 819, 757, 659, 608 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) = 9.95 (bs, 1H), 7.72 (d, *J* = 8.3 Hz, 2H), 7.33 (d, *J* = 8.3 Hz, 2H), 6.72 (t, *J* = 16.9 Hz, 1H), 5.55 (ddt, *J* = 17.1, 10.3, 6.8 Hz, 1H), 5.19–5.10 (m, 2H), 4.18 (d, *J* = 1.3 Hz, 2H), 3.82 (d, *J* = 6.8 Hz, 2H), 2.43 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 168.9, 144.2, 136.5, 131.5, 130.1, 127.4, 125.3, 120.8, 118.1, 60.2, 51.2, 21.7; HRMS (ESI): *m/z calcd.* for $C_{14}H_{17}INO_4S$ $[M + H]^+$: 421.99175, found 421.99126.

(*Z*)-4-(*N*-butyl-4-methylphenylsulfonamido)-3-iodobut-2-enoic acid (3b): Following the general procedure, **3b** was prepared from carboxylic acid **2b**; **3b** was isolated as a white solid (3.20 g, 74 % yield). M.p. 117–119 °C; IR (ATR) ν_{max} = 3156, 1694, 1619, 1598, 1495, 1457, 1418, 1398, 1332, 1273, 1197, 1156, 1009, 900, 759, 740, 696, 659, 564, 512 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) = 8.8 (bs, 1H), 7.70 (d, *J* = 8.2 Hz, 2H), 7.32 (d, *J* = 8.2 Hz, 2H), 6.75 (s, 1H), 4.18 (s, 2H), 3.14 (t, *J* = 7.3 Hz, 2H), 2.43 (s, 3H), 1.43 (quint, *J* = 7.3 Hz, 2H), 1.24 (sext, *J* = 7.3 Hz, 3H), 0.86 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 169.0, 144.0, 136.3, 130.0, 127.3, 125.1, 118.5, 62.1, 49.3, 30.3, 21.6, 20.1, 13.7; HRMS (ESI): *m/z calcd.* for $C_{15}H_{21}INO_4S$ $[M + H]^+$: 438.02305, found 438.02406.

General Procedure for the preparation of lactones 4a-l and 5a-d:

Method A:

A dry Schlenk tube with a Teflon-coated magnetic stirrer was charged with carboxylic acid **3a–b** (0.7 mmol, 1 equiv.) and Et_3N (212 mg, 2.1 mmol, 3 equiv.) in anhydrous DMF (20 mL). CuI (27 mg, 0.14 mmol, 0.2 equiv.) and $PdCl_2(PPh_3)_2$ (25 mg, 0.035 mmol, 0.05 equiv.) were added, and the suspension was stirred for 15 min. Then, the mixture was degassed at 0 °C for 10 min and backfilled with argon. Alkyne (1.4 mmol, 2 equiv.) was added at room temperature, and the reaction mixture was stirred at 55 °C for 12 h. The medium was then cooled to 0 °C and was hydrolyzed with a saturated NH_4Cl aqueous solution (30 mL). Ethyl acetate (30 mL) was added, and the mixture was filtered through a Celite pad. The pad was washed with additional ethyl acetate (3 × 20 mL). The aqueous layer was removed, and the organic layer was washed with water (3 × 10 mL), dried with $MgSO_4$ and concentrated under vacuum. The crude material was purified by flash chromatography on silica gel to give the desired product.

Method B:

A dry Schlenk tube equipped with a Teflon-coated magnetic stirrer was charged with K_2CO_3 (194 mg, 1.4 mmol, 2 equiv.) and carboxylic acid **3a–b** (0.7 mmol, 1 equiv.). Anhydrous DMF (30 mL) was added and the suspension was stirred for 15 min. Then, the mixture was degassed at 0 °C for 10 min and backfilled with argon. Alkyne (1.4 mmol, 2 equiv.) and CuI (163 mg, 0.84 mmol, 1.2 equiv.) were added at room temperature, and the reaction mixture was stirred at 55 °C overnight. The reaction mixture was cooled to room temperature and was partitioned between Et_2O and saturated aqueous NH_4Cl. The organic portions were dried with $MgSO_4$, filtered and concentrated under vacuum. The crude material was purified by flash chromatography on silica gel to give the desired γ-alkylidenebutenolide.

***N*-Allyl-*N*-((2-benzyl-1-butyl-2-hydroxy-5-oxo-2,5-dihydro-1*H*-pyrrol-3-yl)methyl)-4-methylbenzenesulfonamide (4a)**: Following the general procedure, **4a** was prepared from carboxylic acid **3a**; **4a** was isolated as a white solid (194 mg, 70 % yield). M.p. 130–132 °C; IR (ATR) ν_{max} = 3095, 3052, 1757, 1660, 1602, 1573, 1419, 1351, 1317, 1288, 1225, 1175, 1148, 1121, 1091, 917, 817, 663 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.79–7.73 (m, 4H), 7.43–7.33 (m, 5H), 6.20 (s, 1H), 6.03 (s, 1H), 5.56 (ddt, *J* = 16.9, 10.2, 6.6 Hz, 1H), 5.21–5.11 (m, 2H), 4.33 (s, 2H), 3.86 (d, *J* = 6.6 Hz, 2H), 2.45 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 168.5, 155.0, 146.8, 144.3, 136.4,132.6, 131.8, 131.0, 130.2, 129.6, 129.0, 127.4, 120.7, 116.9,

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111.6, 51.1, 42.5, 21.7; HRMS (ESI): *m/z calcd.* for $C_{22}H_{22}NO_4S$ [M + H]$^+$: 396.12641, found 396.12601.

(*Z*)-*N*-Allyl-4-methyl-*N*-((2-(4-methylbenzylidene)-5-oxo-2,5-dihydrofuran-3-yl)methyl)benzenesulfonamide (4b): Following the general procedure, **4b** was prepared from carboxylic acid **3a**; **4b** was isolated as a white solid (186 mg, 65 % yield). M.p. 134–136 °C; IR (ATR) ν_{max} = 3094, 2921, 1759, 1652, 1599, 1513, 1419, 1318, 1148, 941, 883, 815, 665 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.74 (d, *J* = 8.3 Hz, 2H), 7.67 (d, *J* = 8.3 Hz, 2H), 7.35 (d, *J* = 8.3 Hz, 2H), 7.20 (d, *J* = 8.4Hz, 2H), 5.99 (s, 1H), 6.17 (s, 1H), 5.57 (ddt, *J* = 16.9, 10.2, 6.6 Hz, 1H), 5.21–5.10 (m, 2H), 4.33 (s, 2H), 3.86 (d, *J* = 6.2 Hz, 2H), 2.46 (s, 3H), 2.38 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 168.7, 154.8, 146.3, 144.3, 140.1, 136.4, 131.8, 131.0, 130.2, 129.8, 129.7, 127.4, 120.7, 116.5, 111.8, 51.0, 42.5, 21.7, 21.6; HRMS (ESI): *m/z calcd.* for $C_{23}H_{24}NO_4S$ [M + H]$^+$: 410.14206, found 410.14175.

(*Z*)-*N*-Allyl-N-((2-(4-ethylbenzylidene)-5-oxo-2,5-dihydrofuran-3-yl)methyl)-4-methylbenzenesulfonamide (4c): Following the general procedure, **4c** was prepared from carboxylic acid **3a**; **4c** was isolated as a white solid (201 mg, 69 % yield). M.p. 138–140 °C; IR (ATR) ν_{max} = 3092, 3051, 2972, 3937, 1756, 1651, 1610, 1600, 1427, 1316, 1149, 938, 884, 813, 664 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.74 (d, *J* = 8.3 Hz, 2H), 7.69 (d, *J* = 8.3 Hz, 2H), 7.35 (d, *J* = 8.3 Hz, 2H), 7.22 (d, *J* = 8.4Hz, 2H), 6.17 (s, 1H), 5.99 (s, 1H), 5.57 (ddt, *J* = 16.9, 10.1, 6.8 Hz, 1H), 5.21–5.10 (m, 2H), 4.32 (s, 2H), 3.86 (d, *J* = 6.6 Hz, 2H), 2.67 (q, *J* = 8.4 Hz, 2H), 2.46 (s, 3H), 1.24 (t, *J* = 8.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$):δ (ppm) = 168.7, 154.9, 146.3 (2 Cq), 144.3, 136.4, 131.8, 131.1, 130.2, 130.1, 128.5, 127.3, 120.7, 116.4, 111.8, 51.0, 42.5,28.9,21.7, 15.4; HRMS (ESI): *m/z calcd.* for $C_{24}H_{26}NO_4S$ [M + H]$^+$: 424.15771, found 424.15728.

(*Z*)-*N*-Allyl-*N*-((2-(4-methoxybenzylidene)-5-oxo-2,5-dihydrofuran-3-yl)methyl)-4-methylbenzenesulfonamide (4d): Following the general procedure, **4d** was prepared from carboxylic acid **3a**; **4d** was isolated as a white solid (208 mg, 70 % yield). M.p. 140–142 °C; IR (ATR) ν_{max} = 3091, 2971, 2936, 2254, 1754, 1648, 1600, 1512, 1442, 1427, 1344, 1303, 1253, 1152, 1090, 932, 906, 823, 813, 731, 662 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.75–7.72 (m, 4H), 7.34 (d, *J* = 8.3 Hz, 2H), 6.91 (d, *J* = 8.4 Hz, 2H), 6.17 (s, 1H), 5.95 (s, 1H), 5.57 (ddt, *J* = 16.9, 10.2, 6.6 Hz, 1H), 5.21–5.10 (m, 2H), 4.32 (s, 2H), 3.86 (d, *J* = 6.4 Hz, 2H), 3.85 (s, 3H), 2.45 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 168.8, 160.6, 154.8, 145.2, 144.2, 136.2, 132.6, 131.6, 130.1, 127.2, 125.3, 120.5, 115.6, 114.4, 111.5, 55.3, 50.9, 42.5, 21.5; HRMS (ESI): *m/z calcd.* for $C_{23}H_{24}NO_5S$ [M + H]$^+$: 426.13697, found 426.13635.

(*Z*)-*N*-Allyl-*N*-((2-(4-(*tert*-butyl)benzylidene)-5-oxo-2,5-dihydrofuran-3-yl)methyl)-4-methylbenzenesulfonamide (4e): Following the general procedure, **4e** was prepared from carboxylic acid **3a**; **4e** was isolated as a white solid (174 mg, 54 % yield). M.p. 155–157 °C; IR (ATR) ν_{max} = 3095, 3025, 2960, 2868, 1754, 1656, 1598, 1418, 1349, 1323, 1297, 1150, 1126, 1093, 935, 922, 812, 661 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.74 (d, *J* = 8.4 Hz, 2H), 7.71 (d, *J* = 8.3 Hz, 2H), 7.41 (d, *J* = 8.4 Hz, 2H), 7.35 (d, *J* = 8.3 Hz, 2H), 6.17 (s, 1H), 5.99 (s, 1H), 5.57 (ddt, *J* = 16.9, 10.2, 6.6 Hz, 1H), 5.20–5.10 (m, 2H), 4.33 (s, 2H), 3.86 (d, *J* = 6.6 Hz, 2H), 2.46 (s, 3H), 1.33 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 168.7, 154.8, 153.2, 146.4, 144.3, 136.4, 131.8, 130.9, 130.2, 129.8, 127.4, 126.0, 120.7, 116.5, 111.6, 51.0, 42.5, 35.0, 31.2, 21.7; HRMS (ESI): *m/z calcd.* for $C_{26}H_{30}NO_4S$ [M + H]$^+$: 452.18901, found 452.18865.

(*Z*)-*N*-Allyl-*N*-((2-(4-fluorobenzylidene)-5-oxo-2,5-dihydrofuran-3-yl)methyl)-4-methylbenzenesulfonamide (4f): Following the general procedure, **4f** was prepared from carboxylic acid **3a**; **4f** was isolated as a white solid (223 mg, 77 % yield). M.p. 164–166 °C; IR (ATR) ν_{max} = 3096, 1760, 1598, 1508, 1418, 1352, 1316, 1231, 1148, 1123, 944, 920, 883, 817, 664 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.78 (dd, *J* = 8.8, 5.5 Hz, 2H), 7.74 (d, *J* = 8.3 Hz, 2H), 7.35 (d, *J* = 8.4 Hz, 2H), 7.09 (t, *J* = 8.7 Hz, 2H), 6.21 (s, 1H), 6.02 (s, 1H), 5.56 (ddt, *J* = 16.9, 10.3, 6.6 Hz, 1H), 5.20–5.10 (m, 2H), 4.32 (s, 2H), 3.86 (d, *J* = 6.4 Hz, 2H), 2.46 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 168.4, 163.2 (d, $J_{C\text{-}F}$ = 252.0 Hz), 154.8, 146.5 (d, $J_{C\text{-}F}$ = 2.9 Hz), 144.4, 136.3, 133.0 (d, $J_{C\text{-}F}$ = 8.3 Hz), 131.7, 130.2, 128.9 (d, $J_{C\text{-}F}$ = 3.4 Hz), 127.3, 120.8, 116.9, 116.1 (d, $J_{C\text{-}F}$ = 21.8 Hz), 110.5, 51.0, 42.5, 21.7; ^{19}F NMR (282 MHz, $CDCl_3$): δ (ppm) = –109.8; HRMS (ESI): *m/z calcd.* for $C_{22}H_{21}FNO_4S$ [M + H]$^+$: 414.11698, found 414.11658.

(*Z*)-*N*-Allyl-*N*-((2-(4-(dimethylamino)benzylidene)-5-oxo-2,5-dihydrofuran-3-yl)methyl)-4-methylbenzenesulfonamide (4g): Following the general procedure, **4g** was prepared from carboxylic acid **3a**; **4g** was isolated as a white solid (150 mg, 49 % yield). M.p. 122–124 °C; IR (ATR) ν_{max} = 3091, 2919, 1747, 1650, 1606, 1589, 1521, 1445, 1430, 1347, 1319, 1239, 1187, 1149, 1120, 1093, 1061, 1007, 921, 908, 876, 810, 777, 662, 628 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.74 (d, *J* = 8.4 Hz, 2H), 7.68 (d, *J* = 8.3 Hz, 2H), 7.34 (d, *J* = 8.3 Hz, 2H), 6.67 (d, *J* = 8.4 Hz, 2H), 6.13 (s, 1H), 5.83 (s, 1H), 5.58 (ddt, *J* = 16.9, 10.3, 6.8 Hz, 1H), 5.19–5.10 (m, 2H), 4.32 (s, 2H), 3.85 (d, *J* = 6.8 Hz, 2H), 3.04 (s, 6H), 2.45 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 168.4, 155.0, 146.8, 144.3, 136.2, 132.5, 131.7, 130.9, 130.1, 129.5, 128.9, 127.3, 120.7, 116.8, 111.5, 53.5, 51.0, 42.5, 21.6; HRMS (ESI): *m/zc* alcd for $C_{24}H_{27}N_2O_4S$ [M + H]$^+$: 439.16860, found 439.16825.

(*Z*)-*N*-Allyl-*N*-((2-(2-fluorobenzylidene)-5-oxo-2,5-dihydrofuran-3-yl)methyl)-4-methylbenzenesulfonamide (4h): Following the general procedure, **4h** was prepared from carboxylic acid **3a**; **4h** was isolated as a white solid (229 mg, 79 % yield). M.p. 180–182 °C; IR (ATR) ν_{max} = 3095, 2924, 1769, 1758, 1654, 1599, 1487, 1452, 1419, 1351, 1318, 1175, 1148, 1121, 1090, 1011, 935, 919, 815, 776, 763, 664, 638 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 8.20 (td, *J* = 7.8, 1.6 Hz, 1H), 7.74 (d, *J* = 8.4 Hz, 2H), 7.35 (d, *J* = 8.3 Hz, 2H), 7.31–7.28 (m, 1H), 7.19 (td, *J* = 7.5, 4.0 Hz), 1H), 7.11–7.04 (m, 1H), 6.37 (s, 1H), 6.13 (s, 1H), 5.60 (ddt, *J* = 16.9, 10.2, 6.6 Hz, 1H), 5.20–5.13 (m, 2H), 4.31 (d, *J* = 1.3 Hz, 2H), 3.87 (d, *J* = 6.6 Hz, 2H), 2.45 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 168.3, 160.9 (d, $J_{C\text{-}F}$ = 252.7 Hz), 155.6, 147.8, 144.3, 136.3, 131.8, 131.8 (d, $J_{C\text{-}F}$ = 1.6 Hz), 131.1 (d, $J_{C\text{-}F}$ = 8.3 Hz), 130.2, 127.4, 124.4 (d, $J_{C\text{-}F}$ = 3.6 Hz), 120.9, 120.7 (d, $J_{C\text{-}F}$ = 12.1 Hz), 117.3, 115.4 (d, $J_{C\text{-}F}$ = 22.0 Hz), 102.0 (d, $J_{C\text{-}F}$ = 7.8 Hz), 51.4, 42.6, 21.7; ^{19}F NMR (282 MHz, $CDCl_3$): δ (ppm) = –116.0; HRMS (ESI): *m/z calcd.* for $C_{22}H_{21}FNO_4S$ [M + H]$^+$: 414.11698, found 414.11571.

(*Z*)-*N*-Allyl-*N*-((2-(2,4-difluorobenzylidene)-5-oxo-2,5-dihydrofuran-3-yl)methyl)-4-methylbenzenesulfonamide (4i): Following the general procedure, **4i** was prepared from carboxylic acid **3a**; **4i** was isolated as a white solid (247 mg, 82 % yield). M.p. 210–212 °C; IR (ATR) ν_{max} = 3098, 1766, 1645, 1601, 1499, 1435, 1418, 1337, 1275, 1215, 1157, 1142, 1091, 1013, 927, 866, 849, 812, 766, 658, 647 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 8.22 (td, *J* = 8.9, 6.6 Hz, 1H), 7.74 (d, *J* = 8.4 Hz, 2H), 7.35 (d, *J* = 8.4Hz, 2H), 6.98–6.95 (m, 1H), 6.88–6.81 (m, 1H), 6.32 (s, 1H), 6.13 (s, 1H), 5.59 (ddt, *J* = 16.9, 10.1, 6.8 Hz, 1H), 5.21–5.12 (m, 2H), 4.30 (d, *J* = 1.9 Hz, 2H), 3.86 (d, *J* = 6.8 Hz, 2H), 2.46 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 168.1, 163.4 (dd, $J_{C\text{-}F}$ = 254.3, 12.5 Hz), 161.1 (dd, $J_{C\text{-}F}$ = 255.6, 12.0 Hz), 155.5, 147.5 (t, $J_{C\text{-}F}$ = 2.6, 4.0 Hz), 144.4, 136.2, 132.9 (dd, $J_{C\text{-}F}$ = 9.6, 3.0 Hz), 131.8, 130.2, 127.4, 120.9, 117.3, 117.3 (dd, $J_{C\text{-}F}$ = 11.3, 4.0 Hz), 112.4 (dd, $J_{C\text{-}F}$ = 21.2, 3.5 Hz), 104.0 (t, $J_{C\text{-}F}$ = 25.8 Hz), 101.1 (dd, $J_{C\text{-}F}$ = 7.2, 1.9 Hz), 51.4, 42.6, 21.7; ^{19}F NMR

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(282 MHz, $CDCl_3$): δ (ppm) = –105.9 (d, J = 8.7 Hz), –111.5 (d, J = 8.7 Hz); HRMS (ESI): *m/z calcd.* for $C_{22}H_{20}F_2NO_4S$ $[M + H]^+$: 432.10756, found 432.10654.

(*Z*)-*N*-Allyl-*N*-((2-(2-methoxybenzylidene)-5-oxo-2,5-dihydrofuran-3-yl)methyl)-4-methylbenzenesulfonamide (4j): Following the general procedure, **4j** was prepared from carboxylic acid **3a**; **4j** was isolated as a white solid (200 mg, 67 % yield). M.p. 160–162 °C; IR (ATR) ν_{max} = 3110, 3095, 3064, 2927, 2842, 1759, 1742, 1646, 1597, 1588, 1485, 1416, 1318, 1310, 1291, 1247, 1148, 1121, 1092, 935, 871, 811, 657, 605 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) = 8.16 (dd, J = 7.9, 1.6 Hz, 1H), 7.74 (d, J = 8.3 Hz, 2H), 7.36–7.28 (m, 3H), 7.00 (t, J = 7.9 Hz, 1H), 6.88 (d, J = 8.4 Hz, 1H), 6.64 (s, 1H), 5.99–5.97 (m, 1H), 5.62 (ddt, J = 16.9, 10.3, 6.6 Hz, 1H), 5.21–5.12 (m, 2H), 4.36 (d, J = 1.6 Hz, 2H), 3.88 (s, 3H), 3.87 (d, J = 6.8 Hz, 2H), 2.45(s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 168.8, 157.6, 155.7, 146.5, 144.1, 136.3, 131.8, 131.7, 130.9, 130.0, 127.2, 121.4, 121.0, 120.6, 115.9, 110.6, 105.0, 55.6, 51.1, 42.5, 21.6; HRMS (ESI): *m/z calcd.* for $C_{23}H_{24}NO_5S$ $[M + H]^+$: 426.13697, found 426.13549.

(*Z*)-*N*-((2-Benzylidene-5-oxo-2,5-dihydrofuran-3-yl)methyl)-*N*-butyl-4-methylbenzene sulfonamide (4k): Following the general procedure, **4k** was prepared from carboxylic acid **3b**; **4k** was isolated as a white solid (207 mg, 72 % yield). M.p. 128–130 °C; IR (ATR) ν_{max} = 3092, 3052, 2953, 2930, 2871, 1766, 1658, 1602, 1574, 1493, 1452, 1423, 1315, 1223, 1199, 1148, 1091, 1054, 930, 814, 757, 687, 649, 606 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.78 (d, J = 7.3 Hz, 2H), 7.73 (d, J = 8.3 Hz, 2H), 7.43–7.33 (m, 5H), 6.20 (s, 1H), 6.04 (s, 1H), 4.20 (s, 2H), 3.18 (t, J = 7.3 Hz, 2H), 2.45 (s, 3H), 1.46 (quint, J = 7.3 Hz, 2H), 1.25 (sext, J = 7.3 Hz, 2H), 0.85 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 168.5, 155.5,146.8,144.2, 136.1, 132.6, 131.0, 130.1, 129.6, 129.0, 127.3, 116.7, 111.6, 49.1, 44.2, 30.5, 21.7, 20.0, 13.7; HRMS (ESI): *m/z calcd.* for $C_{23}H_{26}NO_4S$ $[M + H]^+$: 412.15771, found 412.15652.

(*Z*)-*N*-Allyl-4-methyl-*N*-((5-oxo-2-(4-(trifluoromethyl)benzylidene)-2,5-dihydrofuran-3-yl)methyl)benzenesulfonamide (4l): Following the general procedure, **4l** was prepared from carboxylic acid **3a**; **4l** was isolated as a white solid (214 mg, 66 % yield). M.p. 210–212 °C; IR (ATR) ν_{max} = 3103, 2867, 1916, 1773, 1652, 1616, 1607, 1418, 1320, 1155, 1111, 1065, 928, 884, 830, 663 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.87 (d, J = 8.4 Hz, 2H), 7.74 (d, J = 8.3 Hz, 2H), 7.63 (d, J = 8.3 Hz, 2H), 7.36 (d, J = 8.4 Hz, 2H), 6.27 (s, 1H), 6.11 (s, 1H), 5.56 (ddt, J = 16.9, 10.2, 6.6 Hz, 1H), 5.20–5.12 (m, 2H), 4.33 (s, 2H), 3.86 (d,J = 6.5 Hz, 2H), 2.46 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 168.0, 154.9, 148.2, 144.5, 136.2, 136.0, 131.7, 131.0, 130.6 (q, $J_{C\text{-}F}$ = 33.6 Hz), 130.3, 127.4, 125.8 (q, $J_{C\text{-}F}$ = 3.7 Hz), 124.0 (q, $J_{C\text{-}F}$ = 273.0 Hz), 120.9, 118.1, 109.7, 51.2, 42.6, 21.7; ^{19}F NMR (282 MHz, $CDCl_3$): δ (ppm) = –62.8; HRMS (ESI): *m/z calcd.* for $C_{23}H_{21}F_3NO_4S$ $[M + H]^+$: 464.11379, found 464.11350.

(*Z*)-*N*-Butyl-*N*-((2-(4-methoxybenzylidene)-5-oxo-2,5-dihydrofuran-3-yl)methyl)-4-methylbenzenesulfonamide (4m): Following the general procedure, **4m** was prepared from carboxylic acid **3b**; **4m** was isolated as a white solid (192 mg, 67 % yield). M.p. 131–133 °C; IR (ATR) ν_{max} = 3145, 2991, 2362, 1784, 1678, 1620, 1561, 1452, 1477, 1335, 1243, 1199, 1137, 1091, 1022, 850, 824, 767, 639, 612 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.76–7.71 (m, 4H), 7.33 (d, J = 8.3 Hz, 2H), 6.91 (d, J = 8.4 Hz, 2H), 6.17 (s, 1H), 5.96 (s, 1H), 4.31 (s, 2H), 3.86 (d, J = 6.4 Hz, 2H), 3.85 (s, 3H), 3.17 (t, J = 7.3 Hz, 2H), 2.44 (s, 3H), 1.45 (quint, J = 7.3 Hz, 2H), 1.25 (sext, J = 7.3 Hz, 2H), 0.84 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 168.8, 160.6, 155.3, 145.4, 144.1, 136.2, 132.8, 130.1, 127.3, 125.4, 115.6, 114.5, 111.7, 55.5, 49.0, 44.1, 30.5, 21.7, 20.0, 13.7; HRMS (ESI): *m/z calcd.* for $C_{25}H_{28}NO_5S$ $[M + H]^+$: 442.16107, found 442.16285.

(*Z*)-*N*-Allyl-4-methyl-*N*-((5-oxo-2-pentylidene-2,5-dihydrofuran-3-yl)methyl)benzene sulfonamide (4n): Following the general procedure, **4n** was prepared from carboxylic acid **3a**; **4n** was isolated as a white solid (50 mg, 19 % yield). M.p. 93–95 °C; IR (ATR) ν_{max} = 3072, 2771, 1756, 1648, 1612, 1573, 1495, 1453, 1433, 1515, 1355, 1225, 1198, 1164, 1158, 1091, 1084, 938, 841, 615 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.70 (d, J = 8.5 Hz, 2H), 7.33 (d, J = 8.5 Hz, 2H), 5.94 (s, 1H), 5.53 (ddt, J = 16.9, 10.1, 6.7 Hz, 1H), 5.42 (t, J = 7.8 Hz, 1H), 5.16–5.07 (m, 2H), 4.20 (d, J = 1.2 Hz, 2H), 3.80 (d, J = 6.7 Hz, 2H), 2.44 (s, 3H),2.36 (d, J = 7.3 Hz, 2H), 1.46–1.30 (m, 4H), 0.90 (t, J = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 168.6, 153.5, 148.2, 144.3, 136.3, 131.8, 130.1, 127.3, 120.6, 117.5, 115.3, 50.9, 42.4, 31.1, 26.1, 22.5, 21.7, 13.9, HRMS (ESI): *m/z calcd.* for $C_{20}H_{26}NO_4S$ $[M + H]^+$: 376.15771, found 376.15527.

(*Z*)-*N*-Allyl-*N*-((2-(cyclohexylmethylene)-5-oxo-2,5-dihydrofuran-3-yl)methyl)-4-methyl benzenesulfonamide (4o): Following the general procedure, **4o** was prepared from carboxylic acid **3a**; **4o** was isolated as a white solid (48 mg, 17 % yield). M.p. 103–105 °C; IR (ATR) ν_{max} = 3095, 3072, 2973, 2950, 2851, 1793, 1662, 1626, 1610, 1415, 1348, 1278, 1193, 1169, 1096, 1094, 988, 862, 626 cm^{-1}; ^1H NMR (300 MHz,$CDCl_3$): δ (ppm) = 7.70 (d, J = 8.3Hz, 2H), 7.32 (d, J = 8.3 Hz, 2H), 5.94 (s, 1H), 5.23 (d, J = 9.7Hz, 1H), 5.54 (ddt, J = 16.9, 10.2, 6.6 Hz, 1H), 5.17–5.06 (m, 2H), 4.18 (d, J = 1.1Hz, 2H), 3.76 (d, J = 7.0 Hz, 2H), 2.74–2.61 (m, 1H), 2.44 (s, 3H), 1.74–1.63 (m, 4H), 1.37–1.08 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 170.3, 162.9, 154.7, 144.1, 136.7, 131.6, 127.3, 120.6, 110.6, 100.7, 51.0, 49.4, 42.4, 30.5, 25.9, 25.8, 21.7; HRMS (ESI): *m/z calcd.* for $C_{22}H_{28}NO_4S$ $[M + H]^+$: 402.17336, found 402.17065.

***N*-Allyl-*N*-((6-isopentyl-2-oxo-2*H*-pyran-4-yl)methyl)-4-methylbenzenesulfonamide (5a)**: Following the general procedure, **5a** was prepared from carboxylic acid **3a**; **5a** was isolated as a white solid (134 mg, 49 % yield). M.p. 187–189 °C; IR (ATR) ν_{max} = 2958, 2872, 1775, 1709, 1647, 1338, 1305, 1184, 1152, 1090, 813, 731, 663 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.70 (d, J = 8.4 Hz, 2H), 7.33 (d, J = 8.4 Hz, 2H), 6.04 (s, 1H), 5.93 (s, 1H), 5.45 (ddt, J = 16.9, 10.3, 6.6 Hz, 1H), 5.13–5.04 (m, 2H), 4.03 (s, 2H), 3.76 (d, J = 6.6 Hz, 2H), 2.46 (t, J = 8.1 Hz, 2H), 2.44 (s, 3H), 1.63–1.48 (m, 3H), 0.92 (d, J = 6.3 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 166.7, 162.8, 154.7,144.1, 136.5, 131.5, 130.1, 127.2, 120.6, 110.4, 102.5, 51.0, 49.3, 35.9, 32.0, 27.8, 22.3, 21.6; HRMS (ESI): *m/z calcd.* for $C_{21}H_{28}INO_4S$ $[M + H]^+$: 390.17336, found 390.17281.

***N*-Allyl-*N*-((6-(3-chloropropyl)-2-oxo-2*H*-pyran-4-yl)methyl)-4-methylbenzene sulfonamide (5b)**: Following the general procedure, **5b** was prepared from carboxylic acid **3a**; **5b** was isolated as a white solid (144 mg, 52 % yield). M.p. 204–206 °C; IR (ATR) ν_{max} = 3162, 2782, 1766, 1719, 1657, 1583, 1475, 1462, 1444, 1375, 1275, 1189, 1154, 1148, 1083, 1074, 939, 851, 715, 616 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.71 (d, J = 8.3 Hz, 2H), 7.34 (d, J = 8.3 Hz, 2H), 6.10 (s, 1H), 5.99 (s, 1H), 5.48 (ddt, J = 16.8, 10.2, 6.9 Hz, 1H), 5.15–5.06 (m, 2H), 4.04 (s, 2H), 3.78 (d, J = 6.9 Hz, 2H), 3.57 (t, J = 6.9 Hz, 2H), 2.66 (t, J = 7.5 Hz, 2H), 2.45 (s, 3H), 2.18–2.09 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 164.2, 162.5, 154.7,144.1, 136.3, 131.5, 130.1, 127.2, 120.6, 110.9, 103.3, 51.1, 49.2, 43.7, 31.0, 29.5, 21.6; HRMS (ESI): *m/z calcd.* for $C_{19}H_{23}ClNO_4S$ $[M + H]^+$: 396.10308, found 396.10293.

***N*-Allyl-*N*-((6-butyl-2-oxo-2*H*-pyran-4-yl)methyl)-4-methylbenzenesulfonamide (5c)**: Following the general procedure, **5c** was prepared from carboxylic acid **3a**; **5c** was isolated as a white solid (158 mg, 60 % yield). M.p. 177–179 °C; IR (ATR) ν_{max} = 3172, 2781, 1776, 1719, 1657, 1583, 1485, 1463, 1443, 1365, 1285, 1179, 1144, 1128, 1071, 1053, 928, 831, 715, 627cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.65 (d, J = 8.4 Hz, 2H), 7.29 (d, J = 8.4 Hz, 2H),

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5.98 (s, 1H), 5.93 (s, 1H), 5.42 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1H), 5.07–5.00 (m, 2H), 3.99 (s, 2H), 3.72 (d, *J* = 7.4 Hz, 2H), 2.39 (s, 3H), 2.41 (t, *J* = 8.4 Hz, 2H), 1.56 (quint, *J* = 7.4 Hz, 2H), 1.30 (sext, *J* = 7.4 Hz, 2H), 0.87 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 166.2, 162.7, 154.7, 143.9, 136.2, 131.4, 129.9, 127.0, 120.4, 110.2, 102.5, 50.9, 49.2, 33.4, 28.8, 22.0, 21.4, 13.6; HRMS (ESI): *m/z calcd.* for $C_{20}H_{26}NO_4S$ $[M + H]^+$: 376.15771, found 376.15511.

***N*-Allyl-*N*-((6-cyclohexyl-2-oxo-2*H*-pyran-4-yl)methyl)-4-methylbenzenesulfonamide (5d)**: Following the general procedure, **5d** was prepared from carboxylic acid **3a**; **5d** was isolated as a white solid (152 mg, 54 % yield). M.p. 134–136 °C; IR (ATR) ν_{max} = 3142, 2884, 1765, 1739, 1667, 1543, 1496, 1432, 1423, 1305, 1280, 1167, 1142, 1108, 1090, 1021, 958, 811, 805, 716, 634 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.70 (d, *J* = 8.4 Hz, 2H), 7.32 (d, *J* = 8.3 Hz, 2H), 5.98 (bs, 1H), 5.93 (bs, 1H), 5.47 (ddt, *J* = 16.8, 10.1, 6.9 Hz, 1H), 5.13–5.04 (m, 2H), 4.03 (s, 2H), 3.77 (d, *J* = 6.9 Hz, 2H), 2.43 (s, 3H), 2.39–2.32 (m, 1H), 1.93–1.69 (m, 6H), 1.39–1.28 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 168.6, 153.5, 148.2, 144.3, 136.3, 131.8, 130.1, 127.3, 120.6, 117.5, 115.3, 50.9, 42.4, 31.1, 26.1, 22.5, 21.7, 13.9, HRMS (ESI): *m/z calcd.* for $C_{22}H_{28}NO_4S$ $[M + H]^+$: 402.17336, found 402.17073.

Acknowledgments

We acknowledge Dr. Frédéric Montigny (Analysis Department, Tours University) for HRMS and Michel Giorgi (Spectropole of Marseille) for all the performed RX analysis.

Keywords: Cyclization · Density functional calculations · Lactones · Regioselectivity · Synthetic methods

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Received: July 26, 2019

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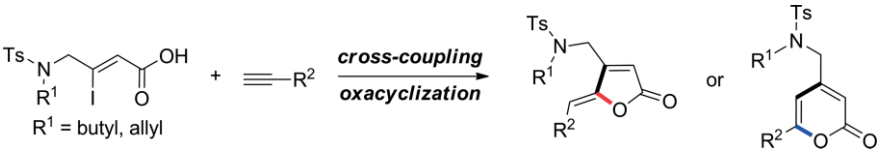
Intramolecular Oxacyclization



Five or six-membered unsaturated lactones bearing an amino group can be synthesized in one-pot reaction. This tandem process involves a Sonogashira-like cross-coupling reaction followed by 5-*exo*-dig or 6-*endo*-dig intramolecular oxacyclization, according to the nature of the alkynes substituent. Furthermore, DFT calculations were performed to analyze the origin of this regioselectivity of cyclization.

DOI: 10.1002/ejoc.201901099

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