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Title: A Formal [3+2] Annulation of β -Oxoamides and 3-Alkyl/arylprop-2-ynyl Sulfonium Salts: Substrate-Controlled Chemoselective Synthesis of Substituted γ -Lactams and Furans

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A Formal [3+2] Annulation of β -Oxoamides and 3-Alkyl- or 3-Aryl-Substituted Prop-2-ynyl Sulfonium Salts: Substrate-Controlled Chemoselective Synthesis of Substituted γ -Lactams and Furans

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Abstract. A substrate-controlled synthesis of substituted γ -lactams and furans has been developed *via* a formal [3+2] annulation of β -oxoamides and 3-alkyl/arylprop-2-ynyl sulfonium salts in the presence of cesium carbonate in a chemoselective manner. This novel protocol features easily

available starting materials, mild reaction conditions, simple execution, and good to excellent yields of products.

Keywords: Annulation; Furans; γ -Lactams; β -Oxoamides; Sulfur ylides

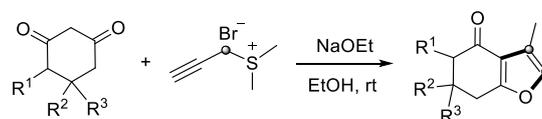
Introduction

Over the past decades, the heterocycles containing γ -lactam or furan skeletons have attracted considerable attention for their presence in numerous natural products and designed molecules along with diverse bioactivities, and widely used in a number of areas ranging from organic synthesis, medicinal chemistry, agrochemistry, to polymer chemistry.^[1-3] In this context, the development of facile and efficient approaches for the synthesis of such five-membered heterocycles through the construction of C–X (X = N, O) bond, in particular from easily available open-chain precursors with flexible substituent patterns, has long been an important topic of organic chemistry and continues to be an active research area.^[4, 5]

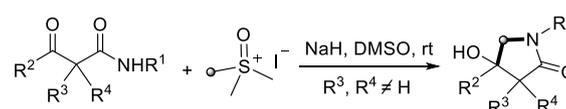
On the other hand, sulfur ylides have emerged as efficient nucleophilic alkylidene-transfer reagents (C_1 and C_2 synthons) in synthetic chemistry, and found wide applications in the preparation of carbo- and heterocycles, including cyclopropanes, epoxides, aziridines, pyrazoles, and pyrrolidines.^[6-8] In the early 1990s, Kanematsu and coworkers developed a convenient synthetic approach for fused 3-methylfuran *via* a formal [3+2] annulation of 1,3-dicarbonyl compounds and prop-2-ynyl sulfonium salts (Scheme 1a), and later applied this furannulation strategy in the total synthesis of some naturally

occurring furanoterpenoids.^[9] Recently, Huang et al. reported the reactions of prop-2-ynyl sulfonium salts with a variety of functionalized arylsulfonamides, by which a series of five-membered aza-heterocycles were obtained and prop-2-ynylsulfonium salts were proved to be versatile C_1 and C_2 synthons.^[10]

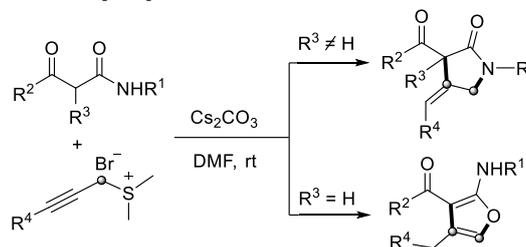
(a) Kanematsu's work: [3+2] annulation



(b) Our previous work: [4+1] annulation



(c) This work: [3+2] annulation

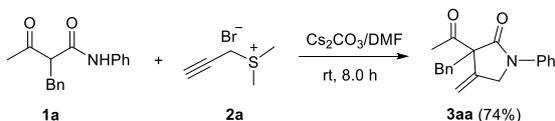


Scheme 1. Sulfur ylide-mediated annulation reactions.

During the course of our studies on the synthesis and applications of varied β -oxoamides and their derivatives,^[11] we achieved efficient synthesis of γ -lactams *via* a formal [4+1] annulation of α,α -dialkyl- β -oxo amides and trimethyl sulfoxonium iodide in the presence of NaH (Scheme 1b)^[12] and synthesis of substituted pyridin-2(1*H*)-ones *via* a formal [4+2] annulation of α -acyl acrylamides and cyanomethyl sulfonium salt in the presence of cesium carbonate (Cs_2CO_3), respectively.^[13] Inspired by these results and our continued research interest in developing new synthetic methods for highly valuable heterocycles, we set out to explore the reactions of β -oxoamides with 3-alkyl/arylprop-2-ynyl sulfonium salts. After a series of detailed investigation, we achieved efficient synthesis of substituted γ -lactams and furans under very mild conditions (Scheme 1c). Herein, we wish to report our experimental results and present a proposed mechanism involved in the formal [3+2] annulation reactions.

Results and Discussion

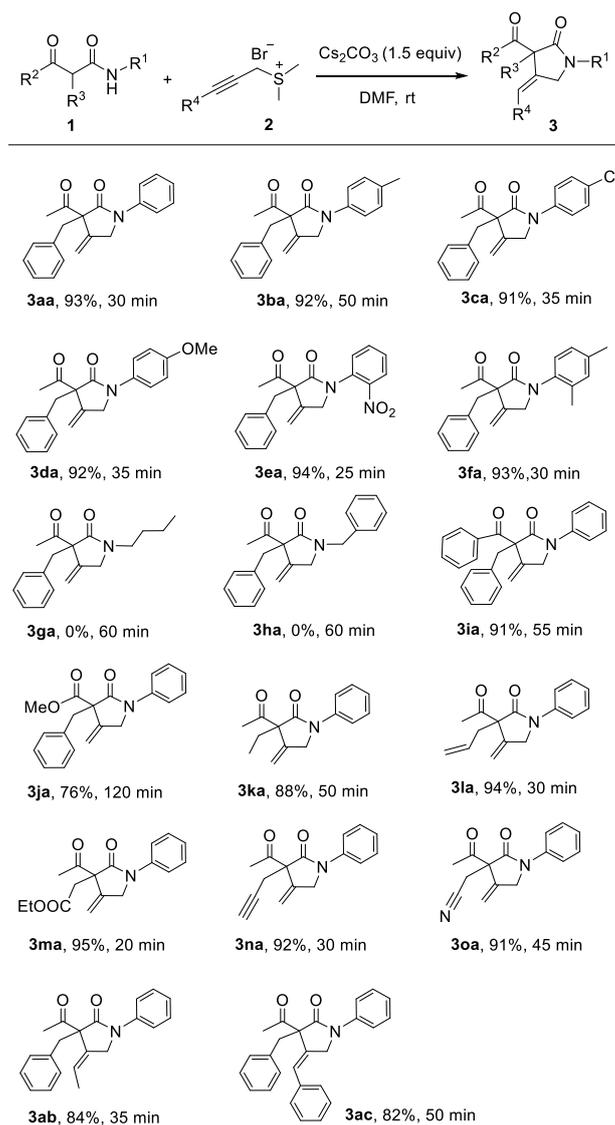
The substrates, α -monosubstituted β -oxoamides **1**, were prepared from commercially available alkyl bromides and α -unsubstituted β -oxoamides in the presence of potassium carbonate (K_2CO_3) in high yields according to a reported procedure.^[11a] Thus, the reaction of 2-benzyl-3-oxo-*N*-phenylbutanamide **1a** and prop-2-ynyl sulfonium salt **2a** (1.0 equiv.) was first attempted in the presence of Cs_2CO_3 (1.0 equiv.) in *N,N*-dimethylformamide (DMF) at room temperature. The reaction proceeded smoothly as indicated by TLC results and furnished a white solid after work-up and purification of the resulting mixture by column chromatography. The product was characterized as 3-acetyl-3-benzyl-4-methylene-1-phenylpyrrolidin-2-one **3aa** on the basis of its spectral and analytical data (Scheme 2).

**Scheme 2.** Reaction of α -monosubstituted β -oxoamide **1a** and prop-2-ynyl sulfonium salt **2a**.

We then briefly examined the effect of different base (Cs_2CO_3 , K_2CO_3 , NaOH, NaOEt, NEt_3 , and DBU), the feed ratio of **1a**/base/**2a**, solvents (DMF, DMSO, DCM, toluene, and acetonitrile), and reaction temperature on the success of the formal [3+2] annulation reaction to **3aa** (for detailed experiments, see Supporting Information). The experimental results revealed that Cs_2CO_3 was the most effective base, and the optimal reaction conditions were obtained when **1a** and **2a** (1.5 equiv.) were treated with Cs_2CO_3 (1.5 equiv.) in DMF at room temperature, whereby the yield of γ -lactam **3aa** reached 93% (Table 1). It should be mentioned that

the structure of **3aa** was unambiguously confirmed by X-ray single crystal analysis (Figure 1).

Having established the optimal conditions for the formal [3+2] annulation process, we aimed to determine its scope and limitation with respect to the substituents R^1 , R^2 and R^3 of α -monosubstituted β -oxoamides **1**. Thus, a series of reactions of **1** and **2** were carried out in the presence of Cs_2CO_3 in DMF at room temperature, and some of the results are summarized in Table 1.

Table 1 Formal [3+2] annulation of α -monosubstituted β -oxoamides **1** and 3-alkyl/arylprop-2-ynyl sulfonium salts **2**^[a]

^[a] Reagents and conditions: **1** (1.0 mmol), **2** (1.5 mmol), Cs_2CO_3 (1.5 mmol), DMF (5.0 mL), rt. Isolated yields of **3** and reaction times are given.

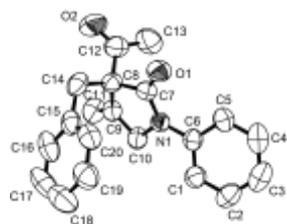


Figure 1. ORTEP drawing of **3aa**.

It was observed that all the reactions of α -benzyl β -oxoamides **1b-f** bearing varied electron-withdrawing or electron-donating substituents on their aryl R^1 groups and **2a** proceeded smoothly to deliver the corresponding γ -lactams **3ba-fa** in excellent yields. Interestingly, the reaction of α -benzyl β -oxoamide **1g** bearing a butyl R^1 group resulted in a complex mixture, in which **3ga** was not even detected. Similar results were obtained when N -benzyl β -oxoamide **1h** was subjected to the identical conditions. The validity of the formal [3+2] annulation is proved to be suitable for α -benzyl β -oxoamides **1i** and **1j** bearing a phenyl or methoxy R^2 group to afford the corresponding γ -lactams **3ia** and **3ja**, respectively. The versatility of this lactam synthesis was further evaluated by performing the reactions of **1k-o** bearing varied R^3 groups and **2a**.

Notably, the reaction of **1a** and but-2-ynyl sulfonium salt **2b** was carried out to furnish a product, which was characterized as (*Z*)-3-acetyl-3-benzyl-4-ethylidene-1-phenylpyrrolidin-2-one **3ab**, and its (*E*)-isomer **3ab'** was not even detected. The *Z*-configuration of **3ab** was established by NOESY spectra (see Supporting Information). The detailed 2D NMR analysis clearly indicated that the reaction of **1a** and **2b** proceeded in a highly stereoselective manner. Similarly, (*Z*)-3-acetyl-3-benzyl-4-benzylidene-1-phenylpyrrolidin-2-one **3ac** was synthesized from **1a** and 3-phenylprop-2-yn-1-yl sulfonium salt **2c**.

The results shown above reveal that benzyl, allyl, alkynyl, ester, cyano, and varied N -aryl amide groups with chloro, methoxy or nitro substituent on benzene ring are well-tolerated under the basic reaction conditions, which demonstrated the efficiency and synthetic value of the transformation of α -monosubstituted β -oxoamides **1** to γ -lactams **3**. By contrast with Kanematsu's work,^[9a] the amide group of **1** preferentially reacts with prop-2-ynyl sulfonium salt **2** over the acyl group of **1** in the present work showed high chemoselectivity of the formal [3+2] annulation process.

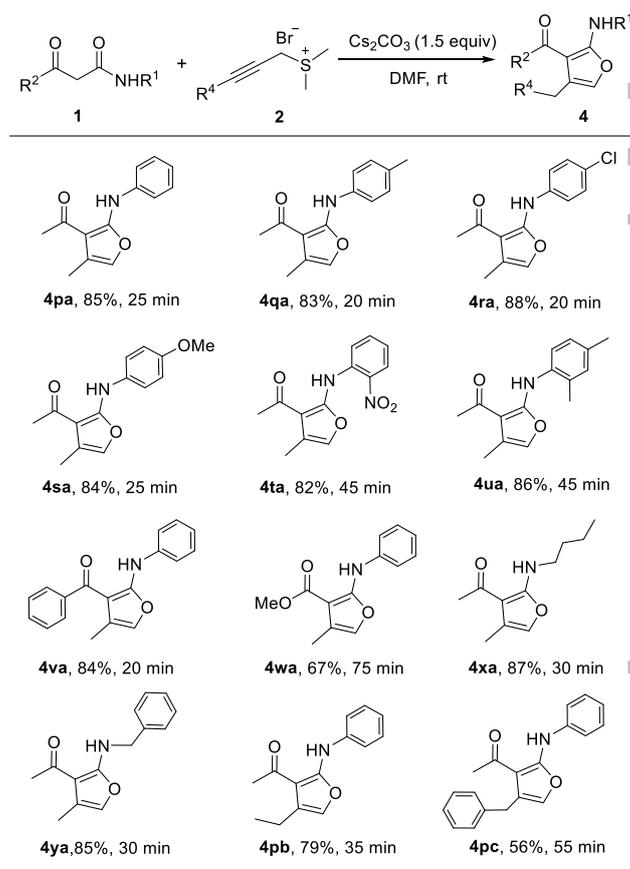


Scheme 3. Reaction of α -unsubstituted β -oxoamide **1p** and prop-2-ynylsulfonium salt **2a**.

To further expand the scope of the formal [3+2] annulation, we intended to examine the reactions of α -unsubstituted β -oxoamides **1** and prop-2-ynyl

sulfonium salts **2** under the identical conditions as for **3aa**. The reaction of 3-oxo-*N*-phenylbutanamide **1p** and **2a** was then performed in the presence of Cs_2CO_3 in DMF at room temperature. A reddish solid was obtained after work-up and purification of the resulting mixture by column chromatography, which was characterized as 1-[4-methyl-2-(phenylamino) furan-3-yl]ethan-1-one **4pa** on the basis of its spectral and analytical data (Scheme 3), and the corresponding γ -lactam **3pa** was not even detected. In the same fashion, a series of α -unsubstituted β -oxoamides **1q-w** bearing varied N -aryl amide groups (CONHR^1) and alkyl, aryl or methoxy R^2 groups reacted with **2a** under the identical conditions afforded the corresponding substituted furans **4qa-wa** in good to high yields. The substituents on the phenyl rings of amides **1** showed little influence on the reactions as both electron-donating and electron-withdrawing groups are well-tolerated. Notably, furans **4xa** and **4ya** were obtained in high yields from the corresponding β -oxoamides **1x** and **1y** bearing a butyl or benzyl R^1 group. The versatility of this furan synthesis was further evaluated by treatment of **1p** with prop-2-ynyl sulfonium salts **2b** and **2c** in the presence of Cs_2CO_3 , respectively.

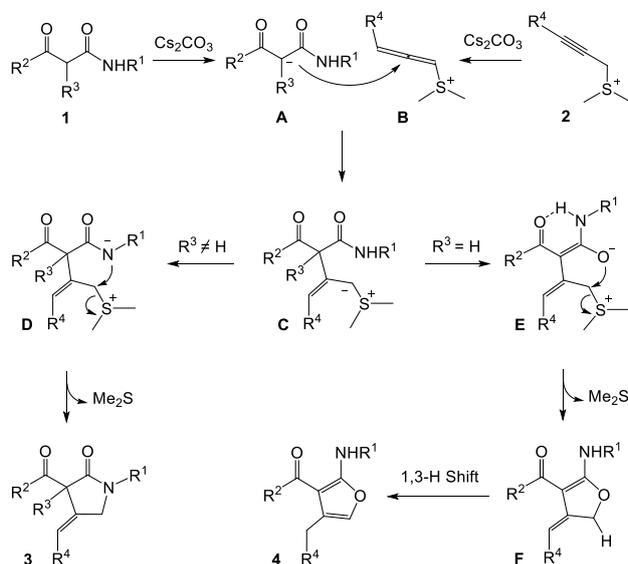
Table 2 Formal [3+2] annulation of α -unsubstituted β -oxoamides **1** and prop-2-ynyl sulfonium salts **2**^[a]



^[a] *Reagents and conditions:* **1** (1.0 mmol), **2** (1.5 mmol), Cs_2CO_3 (1.5 mmol), DMF (5.0 mL), rt. Isolated yields of **4** and reaction times are given.

By comparing the results shown in Table 1 and Table 2, it is easy to conclude that the nature of α -substituent R^3 of β -oxoamides **1** played a critical role in their reactions with prop-2-ynyl sulfonium salts **2** to deliver different products, *i.e.* γ -lactams **3** and furans **4**. Actually, controlling the ambident reactivity of an amide group (CONHR) to form C–N or C–O bond remains a challenging issue in the use of amides in organic transformations.^[14] In the present work, we provided an alternative protocol to achieve the chemoselective C–N or C–O bond formation simply by varying the α -substituent R^3 of the substrate β -oxoamide **1**.^[15]

On the basis of the obtained results together with reported literature,^[6–10] a mechanism is proposed for the formal [3+2] annulation reaction of β -oxoamides **1** and 3-alkyl/arylprop-2-ynyl sulfonium salt **2** as depicted in Scheme 4. In the presence of Cs_2CO_3 , β -oxoamide **1** is quickly deprotonated to a carboanion **A**, and meanwhile prop-2-ynyl sulfonium salt **2** is isomerized to an allenic sulfonium salt **B**.^[9,10] Subsequent conjugated addition of the carboanion **A** to **B** generates intermediate **C**,^[10a] which undergoes a facile proton shift to give *N*-centered or *O*-centered intermediate depending on the nature of α -substituent R^3 of β -oxoamide **1**. For both electronic and steric effects, intermediate **D** is a favorable form when R^3 is not H, wherein the nitrogen anion is particularly stabilized by the adjacent carbonyl and R^1 groups. Then, intramolecular *N*-alkylation of **D** takes place to deliver γ -lactam **3** along with the elimination of dimethyl sulfide.^[8e,16] As such, it is not hard to understand why α -benzyl β -oxoamides **1g** and **1h** bearing a butyl or benzyl R^1 group showed different reaction behavior from other α -monosubstituted β -oxoamides **1** with *N*-aryl amide groups. While R^3 is H, a planar conjugated enolate anion **E** is favored for the formation of intramolecular *N*–H \cdots *O* hydrogen bond,^[17] and the charge on the *O*-atom is easily delocalized within this system.^[18] Enolate **E** undergoes intramolecular *O*-alkylation to afford dihydrofuran **F**,^[19] followed by isomerization through a 1,3-H shift to give the final trisubstituted furan **4**.^[20]



Scheme 4. Plausible mechanism for the formal [3+2] annulation reactions.

Conclusions

In summary, we have described herein a formal [3+2] annulation reaction of β -oxoamides **1** and 3-alkyl/arylprop-2-ynyl sulfonium salts **2** in the presence of Cs_2CO_3 at room temperature, and provided a substrate-controlled synthesis of substituted γ -lactams and furans. The readily available starting materials, mild reaction conditions, simple execution, good to excellent yields of products, and high chemo- and stereoselectivity make this protocol very attractive to academic research and practical applications. Further studies on the mechanism, extension and utilization of the formal [3+2] annulation are currently underway in our laboratory.

Experimental Section

General

All reagents were purchased from commercial sources and used without purification, unless otherwise indicated. ^1H NMR and ^{13}C NMR spectra were recorded at 25 °C at 300 MHz (or 400 MHz) and 75 MHz (or 100 MHz), respectively, with TMS as internal standard. IR spectra (KBr) were recorded on FTIR-spectrophotometer in the range of 400–4000 cm^{-1} . High resolution mass spectra (ESI-Q-TOF/HRMS) were recorded on a mass spectrometer. Melting points were recorded on a TECH X-4 micro-melting point apparatus. All reactions were monitored by TLC with GF254 silica gel-coated plates. The products were isolated by column chromatography on silica gel (300–400 mesh).

General procedure for the synthesis of γ -lactams **3** (**3aa** as an example):

To a mixture of prop-2-ynyl sulfonium salt **2a** (271.6 mg, 1.5 mmol) and Cs_2CO_3 (488.7 mg, 1.5 mmol) in DMF (5.0 mL) was added 2-benzyl-3-oxo-*N*-phenylbutanamide **1a** (267.3 mg, 1.0 mmol). The resulting mixture was stirred at room temperature for 0.5 h, which was then poured into aqueous HCl solution (0.1 N, 50 mL) and extracted with CH_2Cl_2 (3 \times 20 mL). The combined organic phase was washed with water (3 \times 30 mL), dried over anhydrous MgSO_4 , filtered, and evaporated in vacuo. The crude product was purified by column chromatography (silica gel, petroleum ether/ethyl acetate = 6:1) to give **3aa** as a white solid (284.0 mg, 93%).

Analytical data of γ -lactams **3**

3-Acetyl-3-benzyl-4-methylene-1-phenylpyrrolidin-2-one (**3aa**)

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White solid (284.0 mg, 93%), m.p. 125-126 °C; ¹H NMR (300 MHz, CDCl₃): δ 7.32-7.39 (m, 4H), 7.16-7.21 (m, 6H), 5.37 (t, *J* = 2.1 Hz, 1H), 5.26 (t, *J* = 2.4 Hz, 1H), 4.23 (dt, *J*₁ = 13.8 Hz, *J*₂ = 2.1 Hz, 1H), 3.43-3.50 (m, 2H), 3.24 (d, *J* = 13.2 Hz, 1H), 2.25 (s, 3H); ¹³C NMR (75 MHz, CDCl₃): 201.3, 171.7, 139.5, 137.9, 135.8, 130.2, 129.0, 128.1, 126.9, 125.7, 120.8, 112.0, 69.5, 53.0, 40.4, 26.9; IR (KBr): 3030.7, 2924.5, 1714.5, 1687.0, 1661, 1597.7, 1495.1, 1401.8, 907.3, 766.6, 703.2 cm⁻¹; HRMS (ESI) *m/z*: calcd. for C₂₀H₁₉NO₂ [M + Na]⁺: 328.1308, Found: 328.1306.

Crystal data for **3aa**: C₂₀H₁₉NO₂, White crystal, *M* = 305.36, orthorhombic, P2₁2₁2₁, *a* = 7.6446(5) Å, *b* = 13.1672(8) Å, *c* = 16.3981(10) Å, α = 90.00°, β = 90.00°, γ = 90.00°, *V* = 1650.60(18) Å³, *Z* = 4, *T* = 273.15 K, *F*000 = 648.0, *R* = 0.0388 (3056), *wR*2 = 0.1037 (3373). CCDC 1910704 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

3-Acetyl-3-benzyl-4-methylene-1-(*p*-tolyl)pyrrolidin-2-one (3ba)

White solid (293.8 mg, 92%), m.p. 81-82 °C; ¹H NMR (300 MHz, CDCl₃): δ 7.22-7.26 (m, 2H), 7.13-7.16 (m, 7H), 5.35 (t, *J* = 2.1 Hz, 1H), 5.24 (t, *J* = 2.4 Hz, 1H), 4.20 (dt, *J*₁ = 13.2 Hz, *J*₂ = 2.1 Hz, 1H), 3.44 (d, *J* = 13.2 Hz, 2H), 3.23 (d, *J* = 13.2 Hz, 1H), 2.32 (s, 3H), 2.25 (s, 3H); ¹³C NMR (75 MHz, CDCl₃): 201.5, 171.5, 139.7, 135.9, 135.5, 135.4, 130.3, 129.6, 128.1, 126.9, 120.9, 111.9, 69.4, 53.1, 40.4, 26.9, 21.0; IR (KBr): 3034.7, 2924.4, 2869.7, 1711.5, 1686.3, 1661.2, 1511.0, 1394.1, 906.5, 708.1 cm⁻¹; HRMS (ESI) *m/z*: calcd. for C₂₁H₂₁NO₂ [M + Na]⁺: 342.1465, Found: 342.1461.

3-Acetyl-3-benzyl-1-(4-chlorophenyl)-4-methylene pyrrolidin-2-one (3ca)

White solid (309.2 mg, 91%), m.p. 100-101 °C; ¹H NMR (300 MHz, CDCl₃): δ 7.28-7.35 (m, 4H), 7.15 (s, 5H), 5.37 (t, *J* = 2.4 Hz, 1H), 5.26 (t, *J* = 2.4 Hz, 1H), 4.19 (dt, *J*₁ = 13.2 Hz, *J*₂ = 2.4 Hz, 1H), 3.37-3.45 (m, 2H), 3.23 (d, *J* = 13.2 Hz, 1H), 2.24 (s, 3H); ¹³C NMR (75 MHz, CDCl₃): 201.1, 171.9, 139.1, 136.4, 135.6, 130.8, 130.1, 129.1, 128.1, 127.0, 121.7, 112.2, 69.4, 52.8, 40.6, 27.0; IR (KBr): 3063.8, 2974.1, 2924.6, 1714.5, 1687.4, 1661.9, 1495.8, 1454.6, 1395.2, 907.5, 830.2, 702.2 cm⁻¹; HRMS (ESI) *m/z*: calcd. for C₂₀H₁₈ClNO₂ [M + Na]⁺: 362.0918, Found: 362.0920.

3-Acetyl-3-benzyl-1-(4-methoxyphenyl)-4-methylene pyrrolidin-2-one (3da)

White solid (308.6 mg, 92%), m.p. 116-117 °C; ¹H NMR (300 MHz, CDCl₃): δ 7.21 (d, *J* = 9.0 Hz, 2H), 7.18 (m, 5H), 6.86 (d, *J* = 9.0 Hz, 2H), 5.35 (t, *J* = 2.1 Hz, 1H), 5.25 (t, *J* = 2.1 Hz, 1H), 4.18 (dt, *J*₁ = 14.1 Hz, *J*₂ = 1.8 Hz, 1H), 3.79 (s, 3H), 3.39-3.46 (m, 2H), 3.22 (d, *J* = 13.2 Hz, 1H), 2.25 (s, 3H); ¹³C NMR (75 MHz, CDCl₃): 201.5, 171.4, 157.4, 139.8, 135.9, 130.9, 130.3, 128.1, 126.9, 122.8, 114.2, 111.9, 69.2, 55.5, 53.4, 40.4, 26.9; IR (KBr): 3000.9, 2957.7, 2926.3, 1710.8, 1691.4, 1516.1, 1461.7, 1401.4, 1250.8, 1027.9, 833.1, 705.1 cm⁻¹; HRMS (ESI)

m/z: calcd. for C₂₁H₂₁NO₃ [M + Na]⁺: 358.1414, Found: 358.1402.

3-Acetyl-3-benzyl-4-methylene-1-(2-nitrophenyl) pyrrolidin-2-one (3ea)

White solid (329.3 mg, 94%), m.p. 128-129 °C; ¹H NMR (300 MHz, CDCl₃): δ 8.12-8.13 (m, 1H), 7.98-8.05 (m, 2H), 7.53 (t, *J* = 8.4 Hz, 1H), 7.14 (s, 5H), 5.44 (t, *J* = 2.4 Hz, 1H), 5.32 (t, *J* = 2.7 Hz, 1H), 4.29 (dt, *J*₁ = 13.8 Hz, *J*₂ = 1.8 Hz, 1H), 3.43-3.51 (m, 2H), 3.27 (d, *J* = 13.8 Hz, 1H), 2.26 (s, 3H); ¹³C NMR (75 MHz, CDCl₃): 200.6, 172.5, 148.5, 138.9, 138.5, 135.4, 130.0, 129.9, 128.2, 127.2, 125.9, 119.9, 114.6, 112.7, 69.5, 52.6, 40.9, 27.1; IR (KBr): 2930.5, 2873.5, 1712.5, 1694.2, 1527.5, 1390.8, 1353.1, 908.0, 733.5 cm⁻¹; HRMS (ESI) *m/z*: calcd. for C₂₀H₁₈N₂O₄ [M + Na]⁺: 373.1159, Found: 373.1157.

3-Acetyl-3-benzyl-1-(2,4-dimethylphenyl)-4-methylene pyrrolidin-2-one (3fa)

White solid (310.1 mg, 93%), m.p. 96-97 °C; ¹H NMR (300 MHz, CDCl₃): δ 7.26 (s, 5H), 7.02 (s, 1H), 6.93 (d, *J* = 7.8 Hz, 1H), 6.34 (d, *J* = 7.8 Hz, 1H), 5.36 (t, *J* = 2.4 Hz, 1H), 5.31 (t, *J* = 2.7 Hz, 1H), 4.05 (dt, *J*₁ = 14.4 Hz, *J*₂ = 2.1 Hz, 1H), 3.53 (dt, *J*₁ = 14.1 Hz, *J*₂ = 2.1 Hz, 1H), 3.42 (d, *J* = 13.2 Hz, 1H), 3.24 (d, *J* = 13.2 Hz, 1H), 2.31 (s, 3H), 2.28 (s, 3H), 2.01 (s, 3H); ¹³C NMR (75 MHz, CDCl₃): 201.4, 171.4, 140.9, 138.2, 136.2, 135.3, 133.5, 131.8, 130.7, 128.2, 127.6, 127.0, 126.0, 112.0, 68.3, 54.6, 40.3, 27.1, 21.0, 17.8; IR (KBr): 3035.4, 2918.5, 2816.8, 1710.3, 1698.2, 1655.9, 1500.9, 1413.3, 912.1, 711.4 cm⁻¹; HRMS (ESI) *m/z*: calcd. for C₂₂H₂₃NO₂ [M + Na]⁺: 356.1621, Found: 356.1618.

3-Benzoyl-3-benzyl-4-methylene-1-phenylpyrrolidin-2-one (3ia)

White solid (334.4 mg, 91%), m.p. 115-116 °C; ¹H NMR (300 MHz, CDCl₃): δ 7.78 (d, *J* = 7.2 Hz, 2H), 7.49 (t, *J* = 7.2 Hz, 1H), 7.31-7.39 (m, 4H), 7.15-7.26 (m, 8H), 5.32 (t, *J* = 2.1 Hz, 1H), 5.22 (t, *J* = 2.1 Hz, 1H), 4.27 (dt, *J*₁ = 13.8 Hz, *J*₂ = 1.8 Hz, 1H), 3.61 (d, *J* = 12.9 Hz, 1H), 3.41-3.48 (m, 2H); ¹³C NMR (75 MHz, CDCl₃): 194.9, 172.0, 140.9, 137.9, 135.8, 135.4, 132.7, 130.5, 129.0, 128.6, 128.5, 128.1, 127.0, 125.6, 120.9, 112.0, 67.3, 52.9, 42.9; IR (KBr): 2929.7, 2872.5, 1695.6, 1660.1, 1597.2, 1500.8, 1445.9, 1389.1, 914.3, 753.2 cm⁻¹; HRMS (ESI) *m/z*: calcd. for C₂₅H₂₁NO₂ [M + Na]⁺: 390.1465, Found: 390.1451.

Methyl 3-benzyl-4-methylene-2-oxo-1-phenylpyrrolidine-3-carboxylate (3ja)

Yellow oil (244.2 mg, 76%); ¹H NMR (400 MHz, DMSO-*d*₆): δ 7.49 (d, *J* = 8.4 Hz, 2H), 7.35 (t, *J* = 8.4 Hz, 2H), 7.16-7.20 (m, 6H), 5.40-5.41 (m, 2H), 4.46 (d, *J* = 14.4 Hz, 1H), 3.70 (s, 3H), 3.60 (d, *J* = 14.4 Hz, 1H), 3.41 (d, *J* = 13.6 Hz, 1H), 3.29 (d, *J* = 13.6 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃): 170.43, 170.40, 139.9, 138.1, 135.2, 130.5, 128.9, 128.1, 127.0, 125.5, 120.9, 111.2, 62.8, 53.1, 52.7, 40.6; IR (KBr): 3031.6, 2952.9, 2873.9, 1742.7, 1665.1, 1597.9, 1495.8, 1465.6, 1397.3, 1240.9, 909.5, 763.0 cm⁻¹; HRMS (ESI) *m/z*: calcd. for C₂₀H₁₉NO₃ [M + Na]⁺: 344.1257, Found: 344.1254.

3-Acetyl-3-ethyl-4-methylene-1-phenylpyrrolidin-2-one (3ka)

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Yellowish oil (214.1 mg, 88%); ¹H NMR (300 MHz, CDCl₃): δ 7.72 (d, *J* = 8.1 Hz, 2H), 7.43 (t, *J* = 8.1 Hz, 2H), 7.22 (t, *J* = 7.5 Hz, 1H), 5.40 (t, *J* = 2.1 Hz, 1H), 5.16 (t, *J* = 2.1 Hz, 1H), 4.62 (dt, *J*₁ = 14.1 Hz, *J*₂ = 2.1 Hz, 1H), 4.50 (dt, *J*₁ = 14.1 Hz, *J*₂ = 2.1 Hz, 1H), 2.20 (s, 3H), 1.95–2.07 (m, 2H), 0.88 (t, *J* = 7.5 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃): 201.9, 172.0, 139.0, 138.4, 129.2, 125.4, 120.1, 111.5, 68.9, 52.8, 27.4, 26.7, 8.5; IR (KBr): 3065.1, 2970.8, 2879.8, 1714.8, 1598.0, 1504.0, 1392.8, 909.6, 760.0 cm⁻¹; HRMS (ESI) *m/z*: calcd. for C₁₅H₁₇NO₂ [M + Na]⁺: 266.1151, Found: 266.1147.

3-Acetyl-3-allyl-4-methylene-1-phenylpyrrolidin-2-one (3la)

White solid (240.0 mg, 94%), m.p. 50–51 °C; ¹H NMR (300 MHz, CDCl₃): δ 7.68 (d, *J* = 7.8 Hz, 2H), 7.42 (t, *J* = 7.5 Hz, 2H), 7.22 (t, *J* = 7.5 Hz, 1H), 5.60–5.74 (m, 1H), 5.40 (t, *J* = 2.1 Hz, 1H), 5.12–5.19 (m, 2H), 5.05 (dd, *J*₁ = 10.2 Hz, *J*₂ = 1.8 Hz, 1H), 4.59 (dt, *J*₁ = 14.1 Hz, *J*₂ = 2.1 Hz, 1H), 4.44 (dt, *J*₁ = 14.1 Hz, *J*₂ = 2.4 Hz, 1H), 2.86–2.93 (m, 1H), 2.69–2.76 (m, 1H), 2.20 (s, 3H); ¹³C NMR (75 MHz, CDCl₃): 201.1, 171.5, 138.9, 138.3, 132.0, 129.1, 125.5, 120.2, 119.8, 111.9, 68.0, 52.8, 38.8, 26.7; IR (KBr): 2960.0, 2924.7, 1719.2, 1691.6, 1660.2, 1595.3, 1493.6, 1393.1, 918.7, 770.3 cm⁻¹; HRMS (ESI) *m/z*: calcd. for C₁₆H₁₇NO₂ [M + Na]⁺: 278.1151, Found: 278.1152.

Ethyl 2-(3-acetyl-4-methylene-2-oxo-1-phenylpyrrolidin-3-yl)acetate (3ma)

White solid (286.3 mg, 95%), m.p. 57–58 °C; ¹H NMR (300 MHz, CDCl₃): δ 7.71 (d, *J* = 7.8 Hz, 2H), 7.43 (t, *J* = 7.5 Hz, 2H), 7.23 (t, *J* = 7.5 Hz, 1H), 5.35 (s, 1H), 5.16 (s, 1H), 4.61–4.72 (m, 2H), 4.06 (q, *J* = 7.2 Hz, 2H), 3.14–3.31 (m, 2H), 2.19 (s, 3H), 1.17 (t, *J* = 7.2 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃): 199.5, 171.2, 170.5, 139.7, 138.5, 129.2, 125.5, 120.5, 111.2, 65.1, 60.8, 53.0, 38.5, 25.9, 14.1; IR (KBr): 3079.4, 2987.4, 2930.0, 1732.0, 1696.0, 1599.5, 1503.7, 1403.7, 1196.9, 906.0, 767.1 cm⁻¹; HRMS (ESI) *m/z*: calcd. for C₁₇H₁₉NO₄ [M + Na]⁺: 324.1206, Found: 324.1215.

3-Acetyl-4-methylene-1-phenyl-3-(prop-2-yn-1-yl)pyrrolidin-2-one (3na)

White solid (233.0 mg, 92%), m.p. 105–106 °C; ¹H NMR (300 MHz, CDCl₃): δ 7.71 (d, *J* = 8.1 Hz, 2H), 7.44 (t, *J* = 8.1 Hz, 2H), 7.24 (t, *J* = 7.5 Hz, 1H), 5.46 (t, *J* = 2.4 Hz, 1H), 5.25 (t, *J* = 2.7 Hz, 1H), 4.65 (t, *J* = 2.4 Hz, 2H), 2.87–3.02 (m, 2H), 2.21 (s, 3H), 1.91 (t, *J* = 2.4 Hz, 1H); ¹³C NMR (75 MHz, CDCl₃): 199.9, 170.7, 138.7, 138.2, 129.2, 129.1, 125.7, 120.5, 112.3, 79.4, 70.5, 67.1, 53.3, 26.5, 24.5; IR (KBr): 3264.3, 2996.4, 2924.9, 1714.8, 1690.3, 1662.2, 1599.2, 1503.3, 1399.2, 918.9, 760.9, 624 cm⁻¹; HRMS (ESI) *m/z*: calcd. for C₁₆H₁₅NO₂ [M + Na]⁺: 276.0995, Found: 276.0982.

2-(3-Acetyl-4-methylene-2-oxo-1-phenylpyrrolidin-3-yl)acetonitrile (3oa)

Yellow oil (231.4 mg, 91%); ¹H NMR (300 MHz, CDCl₃): δ 7.69 (d, *J* = 8.1 Hz, 2H), 7.45 (t, *J* = 7.8 Hz, 2H), 7.29 (d, *J* = 7.5 Hz, 1H), 5.58 (s, 1H), 5.34 (s, 1H), 4.67–4.80 (m, 2H), 3.00–3.16 (m, 2H), 2.22 (s, 3H); ¹³C NMR (75 MHz, CDCl₃): 197.9, 168.8, 137.7, 136.9, 129.3, 126.3, 120.7,

116.7, 114.4, 64.8, 52.8, 25.9, 22.7; IR (KBr): 3066.2, 2886.8, 2243.5, 1715.2, 1687.3, 1598.4, 1502.2, 1400.5, 903.0, 743.3, 639.1 cm⁻¹; HRMS (ESI) *m/z*: calcd. for C₁₅H₁₄N₂O₂ [M + Na]⁺: 277.0947, Found: 276.0952.

(Z)-3-Acetyl-3-benzyl-4-ethylidene-1-phenylpyrrolidin-2-one (3ab)

White solid (268.3 mg, 84%), m.p. 119–120 °C; ¹H NMR (300 MHz, CDCl₃): δ 7.32–7.40 (m, 4H), 7.13–7.20 (m, 6H), 5.59–5.66 (m, 1H), 4.25 (d, *J* = 13.8 Hz, 1H), 3.41 (d, *J* = 13.5 Hz, 2H), 3.20 (d, *J* = 13.2 Hz, 1H), 2.22 (s, 3H), 1.69 (d, *J* = 6.9 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃): 201.6, 172.1, 138.1, 136.2, 130.7, 130.2, 129.0, 128.0, 126.7, 125.6, 122.4, 121.0, 69.1, 51.1, 40.7, 27.0, 13.8; IR (KBr): 3024.5, 2930.2, 1711.0, 1682.3, 1598.0, 1501.7, 1395.0, 912.5, 778.6 cm⁻¹; HRMS (ESI) *m/z*: calcd. for C₂₁H₂₁NO₂ [M + Na]⁺: 342.1465, Found: 342.1458.

(Z)-3-acetyl-3-benzyl-4-benzylidene-1-phenylpyrrolidin-2-one (3ac)

Yellow oil (312.8 mg, 82%); ¹H NMR (300 MHz, CDCl₃): δ 7.31–7.40 (m, 7H), 7.15–7.22 (m, 8H), 6.50 (s, 1H), 4.45 (dd, *J*₁ = 14.4 Hz, *J*₂ = 2.1 Hz, 1H), 3.73 (dd, *J*₁ = 14.4 Hz, *J*₂ = 2.4 Hz, 1H), 3.52 (d, *J* = 13.2 Hz, 1H), 3.36 (d, *J* = 12.9 Hz, 1H), 2.29 (s, 3H); ¹³C NMR (75 MHz, CDCl₃): 201.4, 171.4, 137.8, 136.0, 135.4, 132.0, 130.2, 129.1, 128.9, 128.3, 128.1, 128.0, 127.0, 126.7, 125.9, 121.3, 70.1, 52.9, 41.3, 27.2; IR (KBr): 2993.9, 2874.3, 1713.4, 1687.5, 1660.7, 1497.3, 1450.8, 1402.5, 903.2, 750.8, 690.9 cm⁻¹; HRMS (ESI) *m/z*: calcd. for C₂₆H₂₃NO₂ [M + Na]⁺: 404.1621, Found: 404.1623.

General procedure for the synthesis of furans 4 (4pa as an example):

To a mixture of prop-2-ynylsulphonium salt **2a** (271.6 mg, 1.5 mmol) and Cs₂CO₃ (488.7 mg, 1.5 mmol) in DMF (5.0 mL) was added 3-oxo-*N*-phenylbutanamide **1p** (177.2 mg, 1.0 mmol). The resulting mixture was stirred at room temperature for 0.5 h, which was then poured into aqueous HCl solution (0.1 N, 50 mL) and extracted with CH₂Cl₂ (3 × 20 mL). The combined organic phase was washed with water (3 × 30 mL), dried over anhydrous MgSO₄, filtered, and evaporated in vacuo. The crude product was purified by column chromatography (silica gel, petroleum ether/ethyl acetate = 8:1) to give **4pa** as a reddish solid (183.0 mg, 85%).

Analytical data of furans 4

1-[4-Methyl-2-(phenylamino)furan-3-yl]ethanone (4pa)

Reddish solid (183.0 mg, 85%), m.p. 57–58 °C; ¹H NMR (300 MHz, CDCl₃): δ 10.51 (s, 1H), 7.30–7.40 (m, 4H), 7.05 (t, *J* = 7.2 Hz, 1H), 6.69 (d, *J* = 0.9 Hz, 1H), 2.40 (s, 3H), 2.20 (d, *J* = 1.2 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃): 192.8, 160.0, 138.0, 130.1, 129.3, 123.0, 118.6, 101.2, 28.7, 11.4; IR (KBr): 2961.4, 2927.8, 1723.7, 1637.7, 1601.2, 1567.5, 1501.7, 1226.8, 943.5, 753.8 cm⁻¹; HRMS (ESI) *m/z*: calcd. for C₁₃H₁₃NO₂ [M + Na]⁺: 238.0838, Found: 238.0843.

1-[4-Methyl-2-(*p*-tolylamino)furan-3-yl]ethanone (4qa)

White solid (190.3 mg, 83%), m.p. 67-68 °C; ¹H NMR (300 MHz, CDCl₃): δ 10.44 (s, 1H), 7.27 (d, *J* = 8.4 Hz, 2H), 7.13 (d, *J* = 8.4 Hz, 2H), 6.66 (d, *J* = 1.2 Hz, 1H), 2.39 (s, 3H), 2.19 (d, *J* = 1.2 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃): 192.5, 160.3, 135.4, 132.7, 129.9, 129.8, 118.8, 118.6, 100.9, 28.6, 20.8, 11.4; IR (KBr): 3020.0, 2972.1, 2922.9, 1643.5, 1588.1, 1465.8, 1380.1, 1243.5, 946.4, 743.0 cm⁻¹; HRMS (ESI) *m/z*: calcd. for C₁₄H₁₅NO₂ [M + Na]⁺: 252.0995, Found: 252.0998.

1-{2-[(4-Chlorophenyl)amino]-4-methylfuran-3-yl} ethanone (4ra)

White solid (215.3 mg, 88%), m.p. 124-125 °C; ¹H NMR (300 MHz, CDCl₃): δ 10.51 (s, 1H), 7.28-7.33 (m, 4H), 6.70 (d, *J* = 0.9 Hz, 1H), 2.40 (s, 3H), 2.20 (d, *J* = 0.9 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃): 193.0, 159.5, 136.6, 130.3, 129.3, 127.8, 119.6, 118.7, 101.4, 28.8, 11.4; IR (KBr): 2957.9, 2928.3, 1630.7, 1611.8, 1590.7, 1498.6, 1223.4, 946.8, 827.6, 720.3 cm⁻¹; HRMS (ESI) *m/z*: calcd. for C₁₃H₁₂ClNO₂ [M + Na]⁺: 272.0449, Found: 272.0442.

1-{2-[(4-Methoxyphenyl)amino]-4-methylfuran-3-yl} ethanone (4sa)

White solid (206.0 mg, 84%), m.p. 93-94 °C; ¹H NMR (300 MHz, CDCl₃): δ 10.37 (s, 1H), 7.30 (d, *J* = 9.0 Hz, 2H), 6.88 (d, *J* = 9.0 Hz, 2H), 6.63 (d, *J* = 0.9 Hz, 1H), 3.80 (s, 3H), 2.39 (s, 3H), 2.19 (d, *J* = 0.9 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃): 192.3, 160.5, 155.8, 131.1, 129.7, 120.6, 118.6, 114.5, 100.6, 55.5, 28.6, 11.4; IR (KBr): 3131.0, 2963.4, 2936.5, 1726.9, 1635.4, 1567.4, 1511.2, 1230.4, 944.8, 731.2 cm⁻¹; HRMS (ESI) *m/z*: calcd. for C₁₄H₁₅NO₃ [M + Na]⁺: 268.0944, Found: 268.0935.

1-[4-Methyl-2-[(2-nitrophenyl)amino]furan-3-yl] ethanone (4ta)

Yellow solid (213.4 mg, 82%), m.p. 125-126 °C; ¹H NMR (300 MHz, CDCl₃): δ 10.72 (s, 1H), 8.36-8.37 (m, 1H), 7.88 (d, *J* = 7.5 Hz, 1H), 7.57 (d, *J* = 8.1 Hz, 1H), 7.47 (t, *J* = 8.1 Hz, 2H), 6.81 (d, *J* = 0.9 Hz, 1H), 2.43 (s, 3H), 2.23 (d, *J* = 0.9 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃): 193.8, 158.6, 149.0, 139.2, 131.0, 130.0, 123.8, 118.7, 117.2, 112.4, 102.1, 28.9, 11.3; IR (KBr): 3037.9, 2967.0, 1633.4, 1610.6, 1531.6, 1397.9, 1342.7, 1231.5, 953.0, 724.5 cm⁻¹; HRMS (ESI) *m/z*: calcd. for C₁₃H₁₂N₂O₄ [M + Na]⁺: 283.0689, Found: 283.0686.

1-{2-[(2,4-Dimethylphenyl)amino]-4-methylfuran-3-yl} ethanone (4ua)

White solid (209.2 mg, 86%), m.p. 150-151 °C; ¹H NMR (300 MHz, CDCl₃): δ 10.51 (s, 1H), 7.62 (d, *J* = 8.7 Hz, 1H), 7.00-7.03 (m, 2H), 6.66 (s, 1H), 2.41 (s, 3H), 2.35 (s, 3H), 2.30 (s, 3H), 2.20 (s, 3H); ¹³C NMR (75 MHz, CDCl₃): 192.4, 160.7, 134.0, 132.8, 131.4, 130.0, 127.3, 126.9, 118.8, 118.6, 101.1, 28.5, 20.8, 18.0, 11.4 cm⁻¹; IR (KBr): 3015.0, 2953.0, 2862.0, 1714.2, 1643.5, 1598.0, 1497.2, 1449.7, 1219.0, 938.3, 727.4 cm⁻¹; HRMS (ESI) *m/z*: calcd. for C₁₅H₁₇NO₂ [M + Na]⁺: 266.1151, Found: 266.1146

[4-Methyl-2-(phenylamino)furan-3-yl](phenyl) methanone (4va)

Yellow solid (232.9 mg, 84%), m.p. 53-54 °C; ¹H NMR (300 MHz, CDCl₃): δ 10.62 (s, 1H), 7.51-7.53 (m, 2H), 7.43-7.48 (m, 5H), 7.36 (t, *J* = 8.1 Hz, 2H), 7.09 (t, *J* = 7.2 Hz, 1H), 6.72 (d, *J* = 0.9 Hz, 1H), 1.62 (d, *J* = 0.9 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃): 191.4, 161.1, 141.3, 137.8, 130.8, 130.3, 129.4, 128.1, 127.3, 123.3, 118.8, 101.1, 11.0; IR (KBr): 3059.9, 2978.8, 2925.3, 1791.7, 1703.0, 1629.1, 1597.9, 1545.3, 1500.1, 1385.4, 945.0, 748.1 cm⁻¹; HRMS (ESI) *m/z*: calcd. for C₁₈H₁₅NO₂ [M + Na]⁺: 300.0995, Found: 300.0993.

Methyl 4-methyl-2-(phenylamino)furan-3-carboxylate (4wa)

Yellow oil (154.9 mg, 67%); ¹H NMR (300 MHz, DMSO-*d*₆): δ 8.93 (s, 1H), 7.28-7.37 (m, 4H), 6.99-7.05 (m, 2H), 3.76 (s, 3H), 2.07 (s, 3H); ¹³C NMR (75 MHz, DMSO-*d*₆): 165.3, 158.4, 139.2, 131.1, 129.6, 122.8, 120.0, 118.8, 91.6, 51.2, 10.5; IR (KBr): 3067.7, 2928.8, 1714.3, 1637.5, 1600.4, 1567.2, 1500.8, 1397.8, 1256.7, 945.6, 751.3, 692.5 cm⁻¹; HRMS (ESI) *m/z*: calcd. for C₁₃H₁₃NO₃ [M + Na]⁺: 254.0788, Found: 254.0790.

1-[2-(Butylamino)-4-methylfuran-3-yl]thanone (4xa)

Reddish solid (169.9 mg, 87%), m.p. 45-46 °C; ¹H NMR (300 MHz, CDCl₃): δ 8.19 (s, 1H), 6.49 (d, *J* = 0.9 Hz, 1H), 3.37 (q, *J* = 6.6 Hz, 2H), 2.30 (s, 3H), 2.12 (d, *J* = 0.9 Hz, 3H), 1.54-1.63 (m, 2H), 1.32-1.45 (m, 2H), 0.93 (t, *J* = 7.2 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃): 191.2, 164.6, 129.0, 118.8, 99.1, 41.2, 32.2, 28.1, 19.9, 13.7, 11.5; IR (KBr): 2960.3, 2932.9, 2873.6, 1641.8, 1565.9, 1455.1, 1397.4, 1078.3 cm⁻¹; HRMS (ESI) *m/z*: calcd. for C₁₁H₁₇NO₂ [M + Na]⁺: 218.1151, Found: 218.1143.

1-(2-(Benzylamino)-4-methylfuran-3-yl)ethanone (4ya)

White solid (194.9 mg, 85%), m.p. 93-94 °C; ¹H NMR (300 MHz, CDCl₃): δ 8.49 (s, 1H), 7.29-7.36 (m, 5H), 6.52 (s, 1H), 4.57 (d, *J* = 6.3 Hz, 2H), 2.32 (s, 3H), 2.14 (s, 3H); ¹³C NMR (75 MHz, CDCl₃): 191.8, 164.2, 138.2, 129.4, 128.7, 127.5, 127.2, 118.9, 99.6, 45.4, 28.3, 11.4; IR (KBr): 2963.5, 2873.0, 1714.5, 1644.7, 1600.9, 1560.4, 1500.3, 1443.2, 1228.3, 940.7, 750.2 cm⁻¹; HRMS (ESI) *m/z*: calcd. for C₁₄H₁₅NO₂ [M + Na]⁺: 252.0995, Found: 252.0991.

1-[4-Ethyl-2-(phenylamino)furan-3-yl]ethanone (4pb)

Yellow solid (181.1 mg, 79%), m.p. 43-44 °C; ¹H NMR (300 MHz, CDCl₃): δ 10.60 (s, 1H), 7.30-7.40 (m, 4H), 7.05 (t, *J* = 7.2 Hz, 1H), 6.66 (s, 1H), 2.64 (q, *J* = 7.2 Hz, 2H), 2.40 (s, 3H), 1.27 (t, *J* = 7.2 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃): 192.7, 160.2, 138.1, 129.4, 129.3, 125.5, 123.0, 118.6, 100.7, 28.8, 19.5, 13.0; IR (KBr): 2961.1, 2930.2, 2874.1, 1636.9, 1602.3, 1567.0, 1500.3, 1449.0, 944.0, 751.0 cm⁻¹; HRMS (ESI) *m/z*: calcd. for C₁₄H₁₅NO₂ [M + Na]⁺: 252.0995, Found: 252.0991.

1-(4-Benzyl-2-(phenylamino)furan-3-yl)ethanone (4pc)

Yellow solid (163.2 mg, 56%), m.p. 129-130 °C; ¹H NMR (400 MHz, DMSO-*d*₆): δ 10.22 (s, 1H), 7.59-7.63 (m, 4H), 7.41 (t, *J* = 7.6 Hz, 2H), 7.30-7.34 (m, 3H), 7.13 (s, 1H), 7.06 (t, *J* = 7.2 Hz, 1H), 2.62 (dd, *J*₁ = 10.8 Hz, *J*₂ = 2.4 Hz, 1H), 2.53 (dd, *J*₁ = 10.8 Hz, *J*₂ = 2.4 Hz, 1H), 2.07 (s, 3H); ¹³C NMR (100 MHz, DMSO-*d*₆): 203.2, 165.2, 139.4, 136.3, 129.2, 129.1, 128.4, 127.7, 125.3, 123.9, 119.7,

119.1, 41.4, 25.7, 18.5; IR (KBr): 3039.2, 2931.2, 1703.4, 1641.2, 1601.3, 1565.0, 1500.8, 1448.2, 1224.1, 943.6, 752.3 cm^{-1} ; HRMS (ESI) m/z : calcd. for $\text{C}_{19}\text{H}_{17}\text{NO}_2$ [M + Na] $^+$: 314.1151, Found: 314.1153.

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FULL PAPER

A Formal [3+2] Annulation of β -Oxoamides and 3-Alkyl/arylprop-2-ynyl Sulfonium Salts: Substrate-Controlled Chemoselective Synthesis of Substituted γ -Lactams and Furans

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