

Note

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Synthesis of aminomethyl derivatives of 5-substituted-3-(prop-2-ynyl)dihydrofuran-2(3H)-ones

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Abstract: An easy approach for the synthesis of various 5-substituted-3-(prop-2-ynyl)dihydrofuran-2(3H)-ones is described. As a method of choice, Mannich aminomethylation of terminal alkynes is adopted. The reaction works well with acyclic and cyclic secondary amines and provides the desired products, with good to very good yields.

Keywords: butanolides; γ -butyrolactones; heterocycles; Mannich aminomethylation; synthesis.

Dedicated to: In memory of our dear friend and colleague Professor Vilik S. Harutyunyan.

1 Introduction

Along with many other structures, γ -butyrolactones serve as important scaffolds for natural compounds [1, 2].

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Structures bearing this fragment are widespread in nature, and a number of such molecules have been isolated so far [3–5]. Several compounds that may be of practical interest in pharmacology and medicine have been obtained from *Gloiopeltis furcata*, *Aspergillus ustus*, *Gardenia sootepensis*, *Sinularia maxima*, *Salvia miltiorrhiza*, and others [6–10]. Other examples include biologically important muricatacin [11], tornabeatins [12], and matairesinol [13] (Fig. 1).

Research on butanolide-containing structures is focused not only on isolation of natural compounds, but also on accessing the appropriate synthetic analogs [14–17]. Considerable interest in these compounds is explained by substantial biological activities that different dihydrofuran-2(3H)-one-based molecules possess including cytotoxic and antimicrobial activities [1, 3, 6–13, 18–20].

Moreover, there are several known experimental and approved drugs bearing a γ -butyrolactone fragment [21, 22] (Fig. 1). Considering all those mentioned above, it is obvious that the development of new methods for the synthesis of lactone-containing compounds is of a distinct interest.

Previously, we carried out numerous elaborations of the methods to get different functionally substituted dihydrofuran-2(3H)-ones [23]. Additionally, follow-up biological investigations of the latter have also been performed to reveal antibacterial activity of the synthesized compounds [24].

Mannich aminomethylation reactions are known to be widely used in fine organic synthesis [25, 26], but there are not many reports on the application of this method in the chemistry of lactones [27–29].

2 Results and discussion

To expand the library of potentially bioactive dihydrofuran-2(3H)-ones and to develop new methods for the

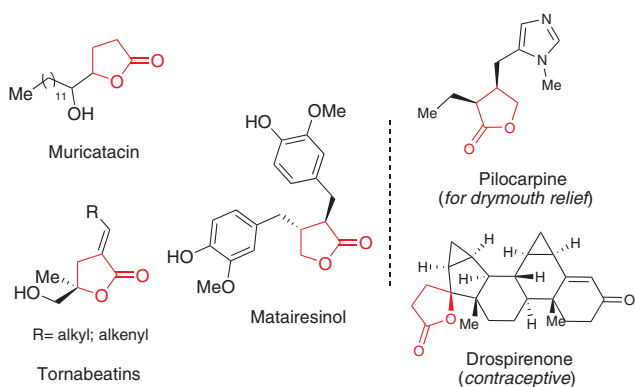


Fig. 1: Selected examples of natural products and pharmaceuticals based on the dihydrofuran-2(3H)-one scaffold.

synthesis of polyfunctionalized butanolides, we chose 5-substituted-3-(prop-2-ynyl)dihydrofuran-2(3H)-ones as an object for research and studied the aminomethylation of the terminal alkyne group by the Mannich reaction. At first, appropriate starting materials **1** were synthesized according to a known procedure [23]. Afterward, syntheses of target compounds **3a–l** were carried out and optimal conditions providing high yields of products were determined (Scheme 1). The interaction of propynylbutanolides **1** with various secondary amines (e.g. dialkylamines, morpholine, piperidine) and paraformaldehyde in the presence of catalytic amounts of CuCl_2 leads to the introduction of the aminomethyl fragment (Table 1).

Moreover, it was established that the reaction of aminomethylation proceeds selectively at the triple bond and, irrespective of the nature of the used amine, provides high yields of the target products.

3 Conclusion

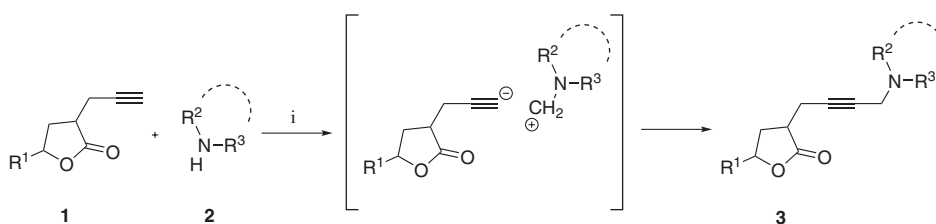
In conclusion, a general method for the synthesis of new dihydrofuran-2(3H)-ones has been elaborated. To

Table 1: Synthesis of **3a–l**.

3	R^1	Amine	Product	Yield (%) ^a
a				79
b				68
c				75
d				73
e				70
f				78
g				69
h				62
i				62
j				66
k				67
l				83

^aYields of isolated products.

transform initial γ -butyrolactones bearing an ethynyl group in the side chain, the Mannich aminomethylation method was used. As a result, a new functional group was successfully introduced into the molecule, with the triple bond remaining unchanged. All compounds were synthesized, with good to very good yields. Our future studies will be directed toward investigations on the biological activity of the synthesized compounds.



Scheme 1: Synthesis of **3a–l**. (i) **1** (1.0 equiv.), amine (1.5 equiv.), paraformaldehyde (1.4 equiv.), CuCl_2 (8.5 mol%), dioxane, 95 °C, 8 h.

4 Experimental section

4.1 General

All chemicals are commercially available and were used without further purification. Thin layer chromatography (TLC) was performed with Silufol UV-254 plates using mixture of AcOH, MeOH, and C₆H₆ (in a ratio of 1:1:4) as eluent, and subsequent development was done by iodine vapor. ¹H NMR data were recorded on a Varian Mercury-300 (300 MHz) spectrometer in [D₆]DMSO. All chemical shifts are given in parts per million. Peak characterization: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. Elemental analyses were performed with a Leco Mikroanalysator – TrueSpec CHNS Micro. Melting points of appropriate oxalate salts were determined on a Boetius Micro heating table and are not corrected.

4.2 General procedure for the synthesis of 3a–l

An oven-dried flask was filled with initial lactone **1** (0.035 mol), the appropriate secondary amine (0.053 mol), 1.6 g of paraformaldehyde (0.05 mol), 0.4 g of CuCl₂ (8.5 mol%), and anhydrous 1,4-dioxane (55 mL). The mixture was stirred at 95–100 °C for 8 h. Afterward, the reaction was cooled to room temperature, and the solvent was distilled off under vacuum. The residue was acidified with hydrochloric acid to pH 2–3 and extracted with ether. The aqueous layer was subsequently alkalized with ammonia solution to pH 7–8 and again extracted with ether. The combined organic phases were washed with water and dried over anhydrous magnesium sulfate. After removal of the solvent, the residue was distilled to give the desired products.

4.2.1 3-(4-(Diethylamino)but-2-ynyl)-5-pentyldihydrofuran-2(3H)-one (3a)

Yield 79%, *R*_f = 0.40, m.p. (oxalate salt) 103–105 °C, b.p. 160–161 °C/1 mmHg. – *n*_D²⁰ = 1.4745. – *d*₄²⁰ = 0.9591. – ¹H NMR (300 MHz, [D₆]DMSO): δ = 0.90 (t, 3H), 1.05 (t, 6H), 1.25 (m, 4H), 1.30 (m, 2H), 1.50 (m, 2H), 1.90 and 2.15 (d, 2H), 2.20 (m, 2H), 2.30 (m, 1H), 2.40 (m, 4H), 2.45 (m, 2H), 3.40 (m, 2H), 4.40 (m, 1H). – C₁₇H₂₉NO₂ (279.42): calcd. C 73.07, H 10.46, N 5.01; found C 73.18; H 10.30; N 5.00.

4.2.2 3-(4-Morpholinobut-2-ynyl)-5-pentyldihydrofuran-2(3H)-one (3b)

Yield 68%, *R*_f = 0.56, m.p. (oxalate salt) 132–134 °C, b.p. 189–190 °C/1 mmHg. – *n*_D²⁰ = 1.4910. – *d*₄²⁰ = 1.0429. – ¹H NMR (300 MHz, [D₆]DMSO): δ = 0.90 (t, 3H), 1.23 (m, 4H), 1.32 (m, 2H), 1.50 (m, 2H), 1.90 and 2.15 (d, 2H), 2.20 (m, 2H), 2.30 (m, 1H), 2.45 (m, 2H), 2.50 (t, 4H), 3.37 (s, 2H), 3.65 (m, 4H), 4.30 (m, 1H). – C₁₇H₂₇NO₃ (293.40): calcd. C 69.59, H 9.28, N 4.77; found: C 69.49, H 9.15, N 4.66.

4.2.3 3-(4-(Diethylamino)but-2-ynyl)-5-hexyldihydrofuran-2(3H)-one (3c)

Yield 75%, *R*_f = 0.67, m.p. (oxalate salt) 65–67 °C, b.p. 181–182 °C/2 mmHg. – *n*_D²⁰ = 1.4720. – *d*₄²⁰ = 0.9350. – ¹H NMR (300 MHz, [D₆]DMSO): δ = 0.88 (t, 3H), 1.05 (t, 6H), 1.25 (q, 4H), 1.30 (m, 4H), 1.55 (m, 2H), 1.90 and 2.15 (d, 2H), 2.25 (m, 2H), 2.30 (m, 1H), 2.40 (m, 4H), 2.50 (m, 2H), 3.40 (m, 2H), 4.30 (m, 1H). – C₁₈H₃₁NO₂ (293.44): calcd. C 73.67, H 10.65, N 4.77; found: C 73.75, H 10.70, N 4.85.

4.2.4 3-(4-(Diethylamino)but-2-ynyl)-5-(propoxymethyl)dihydrofuran-2(3H)-one (3d)

Yield 73%, *R*_f = 0.51, m.p. (oxalate salt) 81–82 °C, b.p. 154–155 °C/1 mmHg. – *n*_D²⁰ = 1.4735. – *d*₄²⁰ = 1.0003. – ¹H NMR (300 MHz, [D₆]DMSO): δ = 0.90 (t, 3H), 1.05 (t, 6H), 1.45 (m, 2H), 1.90 (d, 2H), 2.15 (d, 2H), 2.25 (m, 2H), 2.30 (m, 1H), 2.40 (m, 4H), 2.45 (m, 2H), 3.35 (d, 2H), 3.39 (s, 2H), 3.50 and 3.79 (d, 2H), 4.65 (m, 1H). – C₁₆H₂₇NO₃ (281.39): calcd. C 68.29, H 9.67, N 4.98; found: C 68.35, H 9.55, N 5.10.

4.2.5 3-(4-(Diethylamino)but-2-ynyl)-5-(pentyloxymethyl)dihydrofuran-2(3H)-one (3e)

Yield 70%, *R*_f = 0.55, m.p. (oxalate salt) 93–94 °C, b.p. 170–171 °C/1 mmHg. – *n*_D²⁰ = 1.4730. – *d*₄²⁰ = 0.9803. – ¹H NMR (300 MHz, [D₆]DMSO): δ = 0.92 (t, 3H), 1.05 (t, 6H), 1.40 (m, 2H), 1.50 (m, 4H), 1.95 and 2.15 (d, 2H), 2.20 (m, 2H), 2.30 (m, 1H), 2.40 (m, 4H), 2.45 (m, 2H), 3.35 (s, 2H), 3.40 (d, 2H), 3.50 and 3.75 (d, 2H), 4.60 (m, 1H). – C₁₈H₃₁NO₃ (309.44): calcd. C 69.86, H 10.10, N 4.53; found: C 69.95, H 10.00, N 4.60.

4.2.6 3-(4-(Diethylamino)but-2-ynyl)-5-(butoxymethyl) dihydrofuran-2(3H)-one (3f)

Yield 78%, $R_f = 0.53$, m.p. (oxalate salt) 74–76 °C, b.p. 167 °C/1 mmHg. – $n_D^{20} = 1.4725$. – $d_4^{20} = 0.9893$. – ^1H NMR (300 MHz, $[\text{D}_6]\text{DMSO}$): $\delta = 0.90$ (t, 3H), 1.05 (t, 6H), 1.45 (m, 2H), 1.50 (m, 2H), 1.95 and 2.15 (d, 2H), 2.20 (m, 2H), 2.30 (m, 1H), 2.40 (m, 4H), 2.48 (m, 2H), 3.35 (d, 2H), 3.40 (m, 2H), 3.50 and 3.75 (d, 2H), 4.65 (m, 1H). – $\text{C}_{17}\text{H}_{29}\text{NO}_3$ (295.42): calcd. C 69.12, H 9.89, N 4.74; found: C 69.20, H 9.80, N 4.85.

4.2.7 3-(4-Morpholinobut-2-ynyl)-5-(butoxymethyl) dihydrofuran-2(3H)-one (3g)

Yield 69%, $R_f = 0.44$, m.p. (oxalate salt) 122–124 °C, b.p. 193–194 °C/1 mmHg. – $n_D^{20} = 1.4885$. – $d_4^{20} = 1.0741$. – ^1H NMR (300 MHz, $[\text{D}_6]\text{DMSO}$): $\delta = 0.95$ (t, 3H), 1.50 (m, 4H), 1.90 and 2.15 (d, 2H), 2.25 (m, 2H), 2.30 (m, 1H), 2.45 (m, 2H), 2.50 (m, 4H), 3.35 (d, 2H), 3.40 (m, 2H), 3.48 and 3.75 (d, 2H), 3.65 (m, 4H), 4.60 (m, 1H). – $\text{C}_{17}\text{H}_{27}\text{NO}_4$ (309.40): calcd. C 65.99, H 8.80, N 4.53; found: C 66.05, H 8.75, N 4.60.

4.2.8 3-(4-Morpholinobut-2-ynyl)-5-(propoxymethyl) dihydrofuran-2(3H)-one (3h)

Yield 62%, $R_f = 0.46$, m.p. (oxalate salt) 112–114 °C, b.p. 182–183 °C/1 mmHg. – $n_D^{20} = 1.4915$. – $d_4^{20} = 1.0892$. – ^1H NMR (300 MHz, $[\text{D}_6]\text{DMSO}$): $\delta = 0.93$ (t, 3H), 1.50 (m, 2H), 1.90 (d, 2H), 2.20 (m, 2H), 2.30 (d, 2H), 2.30 (m, 1H), 2.45 (m, 2H), 2.50 (m, 4H), 3.40 (d, 2H), 3.40 (m, 2H), 3.48 and 3.75 (d, 2H), 3.65 (m, 4H), 4.65 (m, 1H). – $\text{C}_{16}\text{H}_{25}\text{NO}_4$ (295.37): calcd. C 65.06, H 8.53, N 4.74; found: C 65.15, H 8.60, N 4.80.

4.2.9 3-(4-(Piperidin-1-yl)but-2-ynyl)-5-(propoxymethyl) dihydrofuran-2(3H)-one (3i)

Yield 62%, $R_f = 0.48$, m.p. (oxalate salt) 111–112 °C, b.p. 175–176 °C/1 mmHg. – $n_D^{20} = 1.4915$. – $d_4^{20} = 1.0399$. – ^1H NMR (300 MHz, $[\text{D}_6]\text{DMSO}$): $\delta = 0.90$ (t, 3H), 1.50 (m, 2H), 1.55 (m, 2H), 1.60 (m, 2H), 1.90 and 2.15 (d, 2H), 2.20 (m, 2H), 2.30 (m, 1H), 2.45 (m, 4H), 2.45 (m, 2H), 3.40 (d, 2H), 3.40 (m, 2H), 3.50 and 3.75 (d, 2H), 4.65 (m, 1H). – $\text{C}_{17}\text{H}_{27}\text{NO}_3$ (293.40): calcd. C 69.59, H 9.28, N 4.77; found: C 69.50, H 9.35, N 4.85.

4.2.10 3-(4-(Piperidin-1-yl)but-2-ynyl)-5-(butoxymethyl) dihydrofuran-2(3H)-one (3j)

Yield 66%, $R_f = 0.42$, m.p. (oxalate salt) 98–100 °C, b.p. 183–184 °C/1 mmHg. – $n_D^{20} = 1.4890$. – $d_4^{20} = 1.0271$. – ^1H NMR (300 MHz, $[\text{D}_6]\text{DMSO}$): $\delta = 0.90$ (t, 3H), 1.45 and 1.50 (m, 4H), 1.55 (m, 4H), 1.60 (m, 2H), 1.90 and 2.15 (d, 2H), 2.20 (m, 2H), 2.30 (m, 1H), 2.43 (m, 2H), 2.50 (m, 4H), 3.35 (d, 2H), 3.40 (m, 2H), 3.50 and 3.75 (d, 2H), 4.70 (m, 1H). – $\text{C}_{18}\text{H}_{29}\text{NO}_3$ (307.43): calcd. C 70.32, H 9.51, N 4.56; found: C 70.40, H 9.45, N 4.60.

4.2.11 3-(4-(Dibutylamino)but-2-ynyl)-5-(butoxymethyl)-dihydrofuran-2(3H)-one (3k)

Yield 67%, $R_f = 0.49$, m.p. (oxalate salt) 84–86 °C, b.p. 184–185 °C/1 mmHg. – $n_D^{20} = 1.4700$. – $d_4^{20} = 0.9617$. – ^1H NMR (300 MHz, $[\text{D}_6]\text{DMSO}$): $\delta = 0.90$ (t, 9H), 1.30 (m, 4H), 1.35 (m, 4H), 1.45 (m, 2H), 1.50 (m, 2H), 1.90 and 2.15 (d, 2H), 2.20 (m, 2H), 2.30 (m, 1H), 2.40 (m, 4H), 2.45 (m, 2H), 3.35 (d, 2H), 3.40 (m, 2H), 3.50 and 3.75 (d, 2H), 4.65 (m, 1H). – $\text{C}_{21}\text{H}_{37}\text{NO}_3$ (351.52): calcd. C 71.75, H 10.61, N 3.98; found: C 71.70, H 10.65, N 4.05.

4.2.12 3-(4-(Dibutylamino)but-2-ynyl)-5-(propoxymethyl)dihydrofuran-2(3H)-one (3l)

Yield 83%, $R_f = 0.54$, m.p. (oxalate salt) 78–79 °C, b.p. 179–180 °C/1 mmHg. – $n_D^{20} = 1.4705$. – $d_4^{20} = 0.9666$. – ^1H NMR (300 MHz, $[\text{D}_6]\text{DMSO}$): $\delta = 0.90$ (t, 9H), 1.30 (m, 4H), 1.35 (m, 4H), 1.45 (m, 2H), 1.90 and 2.15 (d, 2H), 2.30 (m, 1H), 2.20 (m, 2H), 2.40 (m, 4H), 2.45 (m, 2H), 3.35 (d, 2H), 3.40 (m, 2H), 3.50 and 3.75 (d, 2H), 4.65 (m, 1H). – $\text{C}_{20}\text{H}_{35}\text{NO}_3$ (337.50): C 71.18, H 10.45, N 4.15; found: C 71.25, H 10.40, N 4.20.

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