One-pot synthesis of 3-substituted-4H-[1,2,3]triazolo[5,1-c][1,4]oxazin-6(7H)-ones from propargyl alcohols, chloroacetyl chloride, and sodium azide

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Abstract
An efficient, one-pot synthesis of 3-substituted-4H-[1,2,3]triazolo[5,1-c][1,4]oxazin-6(7H)-ones is developed via sequential esterification, substitution, and 1,3-dipolar cycloaddition processes of various propargyl alcohols, chloroacetyl chloride, and sodium azide. This method provides a variety of novel 1,2,3-triazole-fused oxazinones and has several advantages including simple operation, high efficiency, and good-to-excellent product yields (80%–95%) without the need to isolate the ester and azide intermediates.

Keywords
3-substituted-4H-[1,2,3]triazolo[5,1-c][1,4]oxazin-6(7H)-ones, chloroacetyl chloride, one-pot procedure, propargyl alcohols, sodium azide

Introduction
1,2,3-Triazoles are a very important class of heterocyclic compounds, which are widely applied in pharmaceuticals, agrochemicals, dyes, corrosion inhibitors, biochemistries, polymers, and functional materials.¹⁻³ Up to now, many methods based on the azide–alkyne cycloaddition have been developed to prepare 1,2,3-triazole derivatives.⁴⁻¹¹ Among them, one-pot multicomponent reactions in which azides are prepared in situ prior to the cycloaddition are an attractive approach, as time-consuming work-up and purification protocols are minimized and they avoid the handling of potentially explosive azides. Poly-heterocyclic compounds may be used as potential drug candidates because they might exhibit different modes of biological activities compared with their parent ring systems.¹² 1,2,3-Triazoles fused with other heterocyclic moieties have also gained significant importance due to their diverse array of pharmaceutically active functionalities, exhibiting antitumor, antiproliferative, antiviral, and glycosidase inhibitory activities.¹³

The 1,4-oxazinone framework is a well-known heterocyclic moiety, which is widely present in numerous biologically active compounds with potential applications in pharmaceuticals and agrochemicals.¹⁴,¹⁵ Thus, it is not surprising that the incorporation of an oxazinone ring into poly-heterocyclic structures might result in novel and potentially biologically active compounds. To our knowledge, several heterocyclic ring-fused oxazinones such as pyrido[3,2-d][1,2]oxazinones,¹⁶ [3,4-d][1,2]oxazin-4-ones, thieno[3,4-d][1,2]oxazin-4-ones, and pyrido [3,2-d][1,2]oxazin-5-ones¹⁷ have been documented. However, little work relating to the synthesis or bioactivities of the triazolo-fused oxazinones has been reported.¹⁸⁻²⁰ Thus, the development of simple and efficient methods for the construction of the triazolo-fused oxazinones that avoid the isolation of organic azide intermediates are highly desirable. Herein, we report a facile, one-pot, three-step
protocol for the synthesis of 3-substituted-4H-[1,2,3]triazolo[5,1-c][1,4]oxazin-6(7H)-ones involving in situ generation and intramolecular 1,3-dipolar cycloaddition of propargylic azidoacetates. The latter were obtained sequential esterification of propargylic alcohols with chloroacetyl chloride followed by nucleophilic displacement with sodium azide.

Results and discussion

As outlined in Scheme 1, our initial exploratory efforts were devoted to the synthesis of 3-phenyl-4H-[1,2,3]triazolo[5,1-c][1,4]oxazin-6(7H)-one (3a) from 3-phenyl-2-propyn-1-ol (1a), which was treated with chloroacetyl chloride (1.2 equiv.) in the presence of triethylamine to give the intermediate (2a'). Without isolation of the azide 2a', the reaction mixture was further heated for 4 h, whereupon the latter underwent a constrained intramolecular 1,3-dipolar cycloaddition with the alkyne moiety to furnish regioselectively the desired bicyclic compound 3a in 95% yield as the only product. The formation of compound 3a was confirmed by nuclear magnetic resonance (NMR) spectroscopy. The 1H NMR spectrum of 3a has two characteristic singlets corresponding to the methylene protons at 3.90 (–OCH2–) and 4.99 (–COCH2–) ppm, respectively. In the 13C NMR spectrum, the ester carbonyl carbon appeared at 167.8 ppm, and the aromatic carbon signals appeared in the range of 131.9–121.9 ppm.

Not surprisingly, when 1a was reacted with chloroacetyl chloride, other solvents such as toluene, dichloromethane, tetrahydrofuran (THF), DMF, dimethyl sulfoxide (DMSO), or 1,4-dioxane were also applicable for this transformation, while the aprotic, highly polar solvents were not suitable for the subsequent substitution and 1,3-dipolar cycloaddition reactions, as the base for 1 h, followed by the addition of sodium azide. After stirring for 5 h at 100 °C, the desired triazolofused oxazinone 3a was isolated in 91% yield (Table 1, entry 1) as the exclusive product in three-steps.

Finally, to explore the generality and scope of the reaction (Scheme 2), the reaction was carried out with various propargylic alcohols under the optimized reaction conditions and the results are summarized in Table 1.

As observed in Table 1, for all substrates, the reaction proceeded smoothly and the corresponding products 3a–l were obtained in good-to-excellent yields. In addition, no significant difference in the reactivity was found for the examined aromatic propargyl alcohols, including those containing chloro, bromo, methyl, or methoxy substituents on the phenyl ring (Table 1, entries 2–11). It is noteworthy that a higher yield was obtained when R was a methyl group rather than an aryl group (Table 1, entry 12).

In summary, an efficient, one-pot, three-step protocol has been developed for the preparation of 3-substituted-4H-[1,2,3]triazolo[5,1-c][1,4]oxazin-6(7H)-ones with good-to-excellent yields via sequential esterification, substitution and 1,3-dipolar cycloaddition reactions. This procedure should make it possible to rapidly prepare compound libraries for drug discovery programs as it avoids time-consuming and costly isolation and purification protocols involving synthetic intermediates.

Experimental

Propargyl alcohols 1a–k were prepared in good yields by the reactions of aryl bromides with propargyl alcohol in the presence of dichlorobis(triphenylphosphine)palladium according to a reported method. Other reagents and solvents were purchased from commercial suppliers and were used without further purification. The reaction progress was monitored by thin-layer chromatography (TLC) on GF254 silica gel analytical aluminum plates, and the products were visualized under UV spectrophotometer. Column chromatography was performed using silica gel 60 (250–004 mesh) with petroleum ether (bp. 60–90 °C)/ethyl alcohol.

Table 1. Preparation of compounds 3a–l via one-pot three-step reactions.a

| Entry | R | Product (3) | Yield (%)b |
|-------|---|-------------|------------|
| 1     | C6H5 (1a) | 3a | 91 |
| 2     | 4-MeOC6H4 (1b) | 3b | 93 |
| 3     | 2-MeOC6H4 (1c) | 3c | 88 |
| 4     | 4-MeC6H4 (1d) | 3d | 91 |
| 5     | 2-MeC6H4 (1e) | 3e | 86 |
| 6     | 3-MeC6H4 (1f) | 3f | 90 |
| 7     | 4-BrC6H4 (1g) | 3g | 86 |
| 8     | 2-BrC6H4 (1h) | 3h | 82 |
| 9     | 3-BrC6H4 (1i) | 3i | 84 |
| 10    | 4-CIC6H4 (1j) | 3j | 85 |
| 11    | 2-CIC6H4 (1k) | 3k | 83 |
| 12    | Me (1l) | 3l | 95 |

aReaction conditions: 1 (1.0 mmol), chloroacetyl chloride (1.2 mmol), Et3N (3.0 mmol), NaN3 (2.0 mmol), and solvent (10 mL).
b Isolated yield.

Scheme 1. Synthesis of bicyclic triazole 3a from 3-phenyl-2-propyn-1-ol (1a).
acetate as eluent. Melting points were measured using a Beijing-Taike X-4 apparatus without correction. \(^1\)H NMR and \(^13\)C NMR spectra were recorded on a Bruker Avance 400 MHz NMR spectrometer, operating at 400 and 100 MHz, respectively. Fourier-transform infrared spectroscopy (FTIR) analyses were performed with a Perkin-Elmer SP One FTIR spectrophotometer. Microanalyses were performed with a Carlo Erba 1106 Elemental Analyzer.

**General procedure for the preparation of 3-substituted 4H-[1,2,3]triazolo[5,1-c][1,4]oxazin-6(7H)-ones**

Propargyl alcohol 1a–1 (1.0 mmol) was dissolved in dry DMF (10 mL) and then cooled to 0 °C. Anhydrous Et\(_3\)N (0.3 g, 3 equiv.) and chloroacetyl chloride (0.14 g; 1.2 mmol) were added, and the reaction mixture was allowed to stir at room temperature. After the disappearance of the starting materials (monitored by TLC), sodium azide (0.13 g, 2.0 mmol) was added to the reaction mixture. The reaction was heated to 100 °C, stirred for 5 h and then cooled to room temperature. The reaction mixture was treated with water (10 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic extract was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. The residue was subjected to flash column chromatography with petroleum ether/ethyl acetate (5/1) as eluent to afford the desired product 3a–1.

**Scheme 2. One-pot, three-step synthesis of triazolo-fused oxazinone derivatives 3.**

3-(2-Methoxyphenyl)-4H-[1,2,3]triazolo[5,1-c][1,4]oxazin-6(7H)-one (3c): Yellow liquid; \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta 167.9, 160.1, 133.5, 114.0, 113.7, 87.2, 80.9, 55.2, 54.0, 50.0;\) IR (film): 3053, 2944, 2543, 2113, 1749, 1608, 1505, 1160, 1038, 832 cm\(^{-1}\); Anal. calcd for C\(_{13}\)H\(_{11}\)N\(_3\)O\(_2\): C, 58.77; H, 4.52; N, 17.13; found: C, 58.94; H, 4.63; N, 17.20%.

3-(2-Methylphenyl)-4H-[1,2,3]triazolo[5,1-c][1,4]oxazin-6(7H)-one (3d): Yellow liquid; \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta 7.42\) (dd, \(J = 7.5, 1.4\) Hz, 1 H), 7.34–7.30 (m, 1 H), 6.93–6.87 (m, 2 H), 5.08 (s, 2 H), 3.95 (s, 2 H), 3.87 (s, 3 H); \(^13\)C NMR (100 MHz, CDCl\(_3\)): \(\delta 167.8, 160.3, 134.0, 130.6, 128.9, 120.5, 110.7, 85.8, 83.8, 55.8, 54.3, 50.2;\) IR (film): 3042, 2970, 1730, 1605, 1463, 1370, 1262, 1130, 1068, 755 cm\(^{-1}\); Anal. calcd for C\(_{13}\)H\(_{11}\)N\(_3\)O: C, 58.77; H, 4.52; N, 17.13: found: C, 58.96; H, 4.71; N, 17.23%.

3-(2-Methoxyphenyl)-4H-[1,2,3]triazolo[5,1-c][1,4]oxazin-6(7H)-one (3e): Yellow liquid; \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta 7.41\) (dd, \(J = 7.6, 1.1\) Hz, 1 H), 7.23–7.17 (m, 2 H), 7.11 (t, \(J = 7.4\) Hz, 1 H), 5.02 (s, 2 H), 3.89 (s, 2 H), 2.41 (s, 3 H); \(^13\)C NMR (100 MHz, CDCl\(_3\)): \(\delta 167.8, 140.7, 132.3, 129.6, 129.1, 125.6, 121.7, 86.3, 85.9, 54.1, 50.2,\) 20.6; IR (film): 3037, 2984, 1740, 1612, 1510, 1165, 1042, 742 cm\(^{-1}\); Anal. calcd for C\(_{13}\)H\(_{11}\)N\(_3\)O: C, 62.87; H, 4.84; N, 18.33; found: C, 62.94; H, 4.96; N, 18.45%.

3-(2-Methylphenyl)-4H-[1,2,3]triazolo[5,1-c][1,4]oxazin-6(7H)-one (3f): Yellow liquid; \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta 7.31\) (s, 1 H), 7.24 (d, \(J = 7.2\) Hz, 1 H), 7.17 (t, \(J = 8.0\) Hz, 1 H), 7.11 (d, \(J = 7.6\) Hz, 1 H), 4.97 (s, 2 H), 3.88 (s, 2 H), 2.28 (s, 3 H); \(^13\)C NMR (100 MHz, CDCl\(_3\)): \(\delta 167.8, 138.1, 132.5, 129.9, 129.0, 128.3, 121.7, 87.5, 81.8, 53.9, 50.1, 21.1;\) IR (film): 3033, 2987, 1737, 1610, 1508, 1168, 1040, 865, 780, 728 cm\(^{-1}\); Anal. calcd for C\(_{15}\)H\(_{13}\)N\(_3\)O: C, 62.87; H, 4.84; N, 18.33; found: C, 62.96; H, 4.97; N, 18.48%.

3-(2-Bromophenyl)-4H-[1,2,3]triazolo[5,1-c][1,4]oxazin-6(7H)-one (3h): Yellow liquid; \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta 7.45\) (d, \(J = 8.4\) Hz, 2 H), 7.30 (d, \(J = 8.4\) Hz, 2 H), 5.00 (s, 2 H), 3.95 (s, 2 H); \(^13\)C NMR (100 MHz, CDCl\(_3\)): \(\delta 167.7, 133.4, 131.7, 123.4, 120.8, 86.2, 83.2, 53.8, 50.2;\) IR (film): 3068, 2968, 1760, 1568, 1285, 1173, 1035, 820, 690, 558 cm\(^{-1}\); Anal. calcd for C\(_{15}\)H\(_{13}\)Br\(_2\)N\(_3\)O: C, 44.92; H, 2.74; N, 14.29; found: C, 45.13; H, 2.92; N, 14.48%.
3-(3-Bromophenyl)-4H-[1,2,3]triazolo[5,1-c][1,4]oxazin-6(7H)-one (3j): Yellow liquid; \(^1H\) NMR (400 MHz, CDCl\(_3\)): \(\delta 7.58\) (s, 1 H), 7.45 (d, \(J = 6.80\) Hz, 1 H), 7.37–7.35 (m, 1 H), 7.16 (t, \(J = 8.00\) Hz, 1 H), 5.00 (s, 2 H), 3.95 (s, 2 H); \(^{13}C\) NMR (100 MHz, CDCl\(_3\)): \(\delta\) 167.7, 135.1, 133.2, 128.7, 120.3, 86.1, 83.1, 53.8, 50.1; IR (film): 3061, 2982, 1755, 1600, 1558, 1385, 1165, 1040, 739 cm\(^{-1}\); Anal. calcd for C\(_{11}\)H\(_8\)N\(_3\)O\(_2\)Cl: C, 47.28; H, 4.85; N, 27.62%; found: C, 47.18; H, 4.85; N, 27.62%.

3-(3-Chlorophenyl)-4H-[1,2,3]triazolo[5,1-c][1,4]oxazin-6(7H)-one (3k): Yellow liquid; \(^1H\) NMR (400 MHz, CDCl\(_3\)): \(\delta 7.47\) (dd, \(J = 7.6, 1.60\) Hz, 1 H), 7.38 (d, \(J = 8.00\) Hz, 1 H), 7.28–7.20 (m, 2 H), 5.06 (s, 2 H), 3.95 (s, 2 H); \(^{13}C\) NMR (100 MHz, CDCl\(_3\)): \(\delta\) 167.7, 135.1, 133.2, 130.1, 129.3, 126.5, 121.8, 87.2, 83.9, 53.8, 50.2; IR (film): 3061, 2982, 1755, 1600, 1558, 1165, 1040, 739 cm\(^{-1}\); Anal. calcd for C\(_{11}\)H\(_8\)N\(_3\)O\(_2\)Br: C, 44.92; H, 2.74; N, 14.41%; found: C, 45.14; H, 2.92; N, 14.41%.

3-Methyl-4H-[1,2,3]triazolo[5,1-c][1,4]oxazin-6(7H)-one (3l): Yellow liquid; \(^1H\) NMR (400 MHz, CDCl\(_3\)): \(\delta 7.48\) (dd, \(J = 8.0, 0.8\) Hz, 1 H), 7.38 (dd, \(J = 7.6, 1.6\) Hz, 1 H), 7.17 (dd, \(J = 7.4, 1.0\) Hz, 1 H), 7.10 (dd, \(J = 7.8, 1.8\) Hz, 1 H), 4.97 (s, 2 H), 3.87 (s, 2 H); \(^{13}C\) NMR (100 MHz, CDCl\(_3\)): \(\delta\) 167.7, 133.8, 132.5, 130.2, 127.1, 125.7, 124.0, 85.6, 85.7, 53.9, 50.2; IR (film): 3066, 2965, 1756, 1565, 1284, 1175, 1032, 780, 675, 555 cm\(^{-1}\); Anal. calcd for C\(_{11}\)H\(_8\)N\(_3\)O\(_2\)Br: C, 45.19; H, 2.90; N, 14.45%.

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Supplemental material
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