

Synthesis One Pot of Alkyne-2-Chloroquinoline via a Passerini Reaction [†]

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Abstract: A series of six new alkyne-2-chloroquinolines were synthesized in moderate yields (40%–65%) via the Passerini three-component reaction (P-3CR) under mild green conditions. The P-3CR takes place when a carboxylic acid, an oxo compound (aldehyde or ketone), and an isocyanide react to give α -acyloxy carboxamides. Recently it has been reported that small molecules containing alkynes promote interactions with different proteins in cells facilitating the detection or identification of protein targets.

Keywords: multicomponent reactions; Passerini reaction; 2-chloroquinolin-3-carboxaldehyde; alkynes

1. Introduction

Multicomponent reactions (MCRs) are well established as a powerful tool for the rapid construction of novel, complex, and structurally diverse compounds from relatively simple or commercially available starting materials [1]. High atom economy, chemical efficiency, and convergence and very high bond-forming-index are typical features of such one-pot processes with at least three different starting materials. In particular, isocyanide-based multicomponent reactions (IMCR) have become an emerging field of interest in the last decade and there has recently been a focus toward the construction of heterocycles and polyheterocycles via MCRs [2,3]. In 1921, Passerini reported the first IMCR, the Passerini three-component reaction (P-3CR), in which a carboxylic acid, an oxo compound, and an isocyanide react efficiently to generate α -acyloxy carboxamides [4]. This IMCR is typically carried out with high concentrations of starting materials in an aprotic solvent [5]. The stereo-electronic nature of the starting materials has a direct influence on reaction times and commonly a few hours to several days are required.

The P-3CR reaction is the best method for the synthesis of α -acyloxy carboxamides, which are analogues of depsipeptides, which in turn are analogues of peptides. Depsipeptides incorporate an ester functionality and can show promising biological activity (Figure 1) [6].

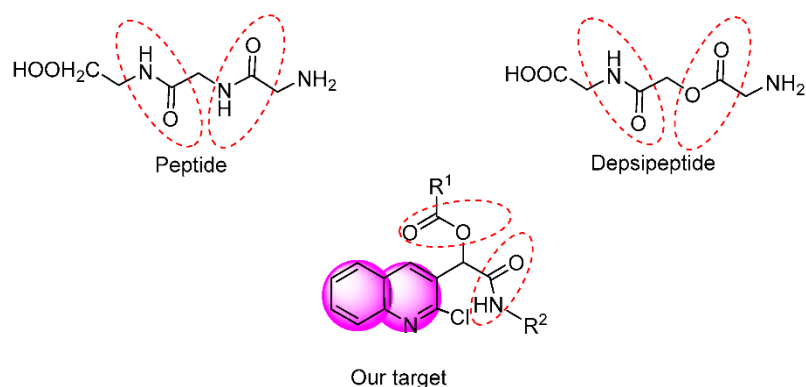


Figure 1. The structures of peptide, depsipeptide, and our target.

Nowadays, the design and development of green methodologies and/or strategies is attracting considerable attention. Therefore, more efficient and environmentally friendly methodologies for the Passerini reaction are highly desirable and several variants of conventional protocols have been achieved to improve yield and decrease environmental impact and reaction times. In this context this reaction has been recently reported in aqueous solution [7], ionic liquid [8,9], eutectic solvents [10], and under solvent-free conditions [11]. It is a highlight that alternative energy sources such as mechanochemistry [12], microwaves [13], and ultrasound [14] have been little explored in the P-3CR.

Given our ongoing interest in MCRs and considering the high potential of the Passerini reaction in the synthesis of bioactive molecules, herein we report a new protocol for performing an efficient functionalization of 2-chloroquinolin-3-carbaldehyde using propynoic and 4-pentynoic acid as orthogonal bifunctional reagents, resulting in a highly functionalized Passerini-adduct that has enabled subsequent post-transformations. In this respect, the alkyne group has proved ideal for post-transformation taking place after the multicomponent step.

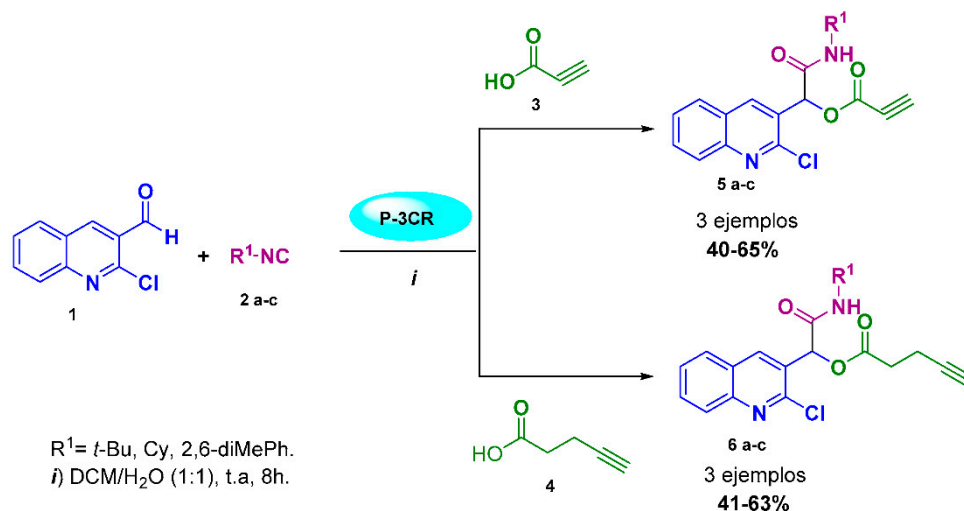
The use of carboxylic acids that contain an alkyne group in their structure has been little explored in the P-3CR [15,16]. Herein we reported a contribution in this area, with the complex terminal alkyne generated via P-3CR.

2. Results and Discussion

Our research was directed towards the efficient synthesis of highly functionalized heterocycles, such as alkyne-2-chloroquinoline, in moderate yields (40%–65%) via the Passerini three-component reaction (P-3CR), under mild green conditions.

The IMCR synthetic methodology involved a sequential combination of 2-chloroquinoline-3-carboxaldehyde (**1**), one equivalent of propynoic acid (**3**) or pentynoic acid (**4**) and one equivalent of isocyanide (**2a–c**) in a DCM/H₂O (1:1) mixture. It is well documented that the use of binary system mixtures that involve volatile and green organic solvents can be used to improve yields and decrease reaction times [17] (Scheme 1).

We began our investigation by optimizing the Passerini reaction, selecting 2-(tert-butylamino)-1-(2-chloroquinolin-3-yl)-2-oxoethyl propiolate as our model target to optimize the one-pot process. First, the formation of P-3CR product was attempted by the simple mixing of 2-chloroquinoline-3-carbaldehyde, propynoic acid, and tertbutyl isocyanide. The reactions using the solvent mixture MeOH/H₂O (1:1) and surfactant (entries 1 and 7, Table 1) resulted in low yields, while the same reaction with DCM/H₂O (1:1) mixture at room temperature for 8 h was more fruitful (entry 8, Table 1). The reactions were monitored by thin-layer chromatography (TLC) and the isolated product was confirmed by ¹H y ¹³C Nuclear magnetic resonance spectroscopy (NMR).

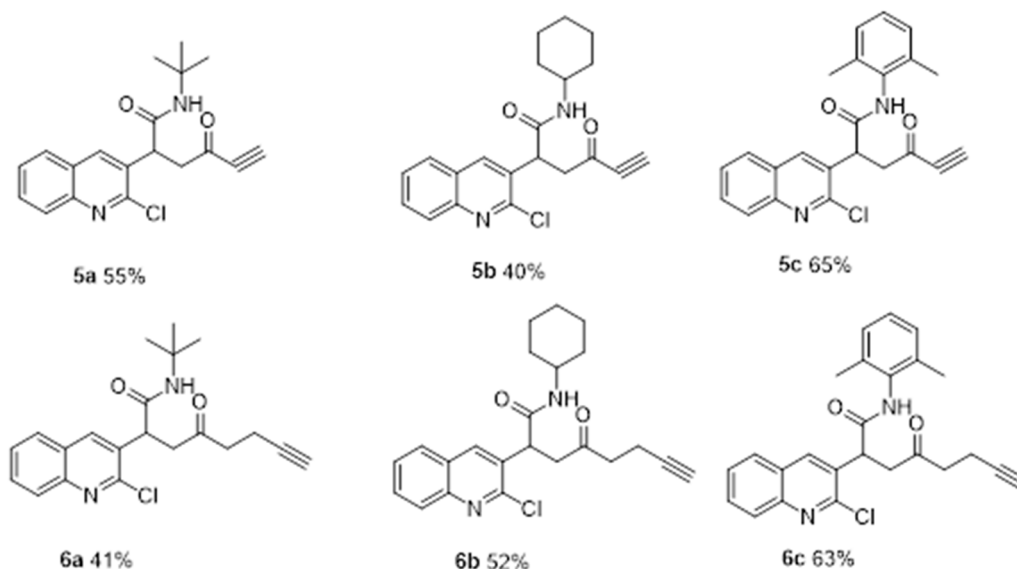


Scheme 1. Strategy for the synthesis of alkyne-2-chloroquinoline.

Table 1. Reaction optimizing conditions of 2-(tert-butylamino)-1-(2-chloroquinolin-3-yl)-2-oxoethyl propiolate (5a).

| Entry | Solvent | Temperature (°C) | Time (h) | Yield (%) |
|-------|-----------------------------|------------------|----------|-----------|
| 1 | MeOH/H ₂ O (1:1) | r.t | 8 | 17 |
| 2 | MeOH/H ₂ O (1:1) | r.t USI | 3 | 21 |
| 3 | H ₂ O | r.t | 24 | n.r |
| 4 | H ₂ O | r.t USI | 3 | n.r |
| 5 | Solvent Free | r.t USI | 3 | n.r |
| 6 | Solvent Free | 60 USI | 3 | n.r |
| 7 | Surfactant (1M) | r.t USI | 3 | 12 |
| 8 | DCM/H ₂ O (1:1) | r.t | 8 | 55 |

Using optimized conditions, the series of six new alkyne-2-chloroquinolines was synthesized (Scheme 2). The versatility of the developed methodology was examined using the different isocyanide moieties aryl and alkyl and two acids (propynoic and pentynoic). The respective products **5a–c** and **6a–c** were obtained in moderate to good yields (40%–65%).



Scheme 2. Substrate scope.

3. Experimental Section

General information. ^1H and ^{13}C NMR spectra were acquired on a 500 MHz spectrometer. The solvent for NMR samples was CDCl_3 . Chemical shifts were reported in parts per million (δ/ppm). Internal reference for NMR spectra was tetramethylsilane at 0.00 ppm. Coupling constants were reported in Hertz (J/Hz). Multiplicities of the signals were reported using the standard abbreviations: singlet (s), doublet (d), triplet (t), quartet (q), and multiplet (m). NMR spectra were analyzed using the MestreNova software version 10.0.1-14719. The reaction progress was monitored by TLC and the spots were visualized under UV light (254 or 365 nm). Flash column chromatography was performed using silica gel (230–400 mesh) and mixtures in different proportions of hexanes with ethyl acetate as mobile phase. Chemical names and drawings were obtained using the ChemBioDraw Ultra 13.0.2.3020 software package.

General method: 2-Chloroquinoline-3-carboxaldehyde (0.365 mmol, 1.0 equivalent), carboxylic acid **3** or **4** (0.365 mmol, 1.0 equivalent), and isocyanide **2a–c** (0.365 mmol, 1.0 equivalent) were dissolved in $\text{DCM}/\text{H}_2\text{O}$ (1:1) mixture and placed in a 10 mL sealed vial. The mixture was stirred at room time for 8 h. Then, the solvent was removed to dryness and the crude was purified by silica-gel column chromatography to afford the products **5a–c** and **6a–c**.

Spectral data

1-(2-Chloroquinolin-3-yl)-2-((2,6-dimethylphenyl)amino)-2-oxoethyl propiolate (**5c**). White solid (111.0 mg, 65%); $R_f = 0.32$ (Hexanes-EtOAc = 7/3 *v/v*); ^1H NMR (500 MHz, CDCl_3) δ 8.49 (s, 1H), 8.06–8.03 (d, $J = 8.4$ Hz, 1H), 7.89–7.85 (m, 1H), 7.81–7.73 (m, 2H), 7.63–7.59 (m, 1H), 7.12–7.08 (m, 1H), 7.06–7.03 (m, 2H), 6.7 (s, 1H), 2.83–2.76 (m, 2H), 2.66–2.58 (m, 2H), 2.18 (s, 6H), 1.94 (t, $J = 2.6$ Hz 1H); ^{13}C NMR (126 MHz, CDCl_3) δ 170.5, 165.2, 148.7, 147.6, 139.6, 135.5, 132.5, 131.5, 128.4, 128.3, 128.0, 127.8, 127.7, 127.0, 126.9, 82.4, 73.0, 69.7, 33.3, 18.4, 14.4. (Figures 2–4).

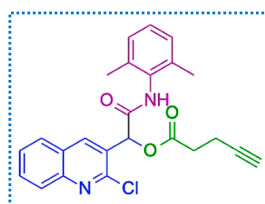


Figure 2. Compound **5c**.

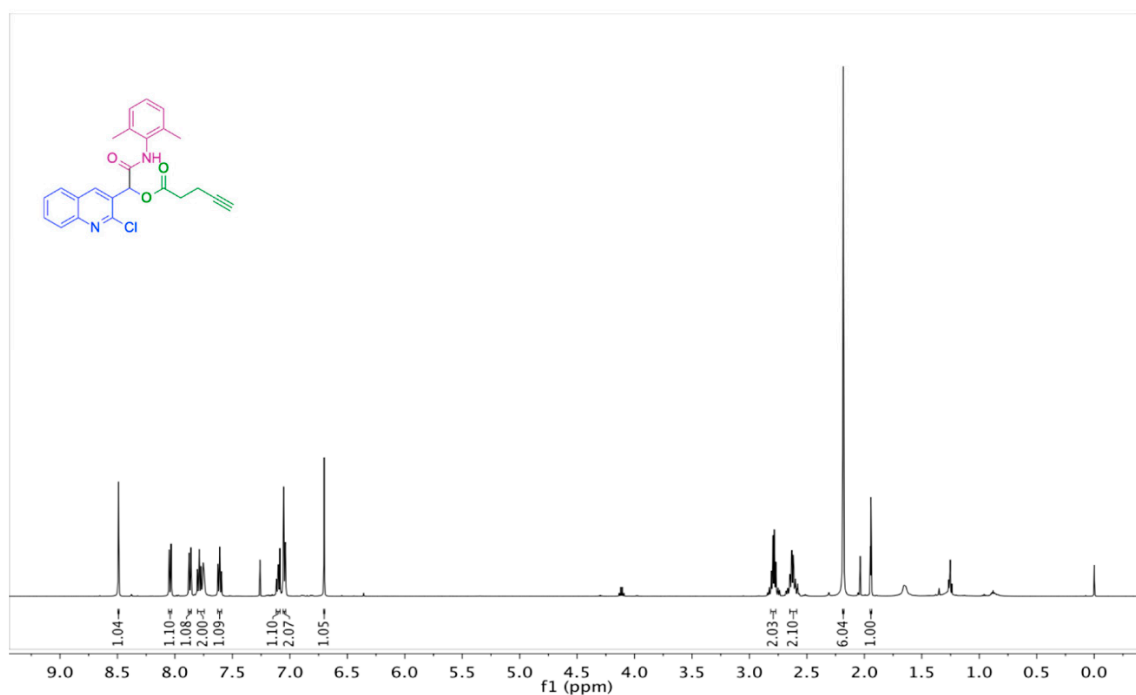


Figure 3. ^1H NMR spectrum of compound 5c.

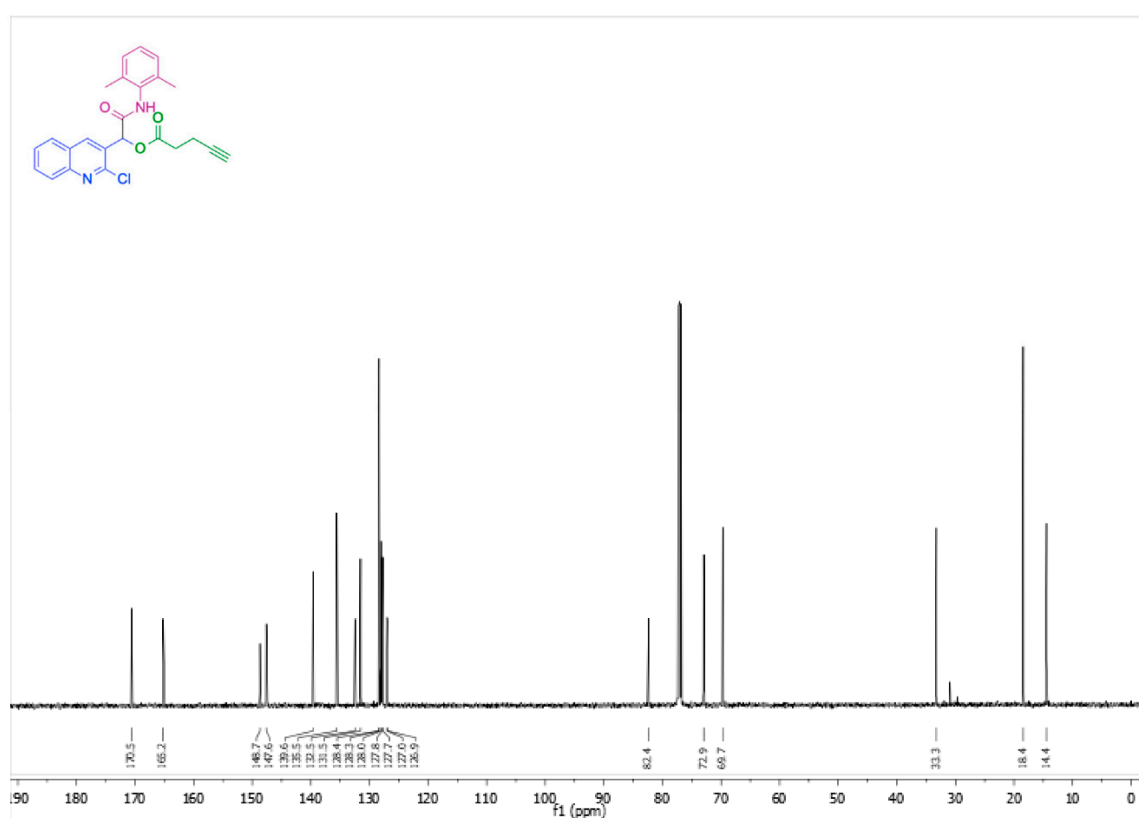


Figure 4. ^{13}C NMR spectrum of compound 5c.

4. Conclusions

A series of six new alkyne-2-chloroquinolines were synthesized in moderate to good yields (40%–65%) via the Passerini three-component reaction (P-3CR) under mild green conditions.

Author Contributions: All authors contributed equally to this work.

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Conflicts of Interest: The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

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