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Synthesis of α-Acyloxycarboxamides via Passerini Reaction †

Sandra C. Ramírez-López and Rocío Gámez-Montaño *

[1] Departamento de Química, Universidad de Guanajuato, Noria Alta S/N, Col. Noria Alta, C.P., Guanajuato 36050, Gto., México

* Correspondence: rociogm@ugto.mx; Tel.: +52-473-73-20006 (ext. 8191)

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Abstract: The Passerini products were synthesized via a facile, efficient, and environmentally friendly strategy under catalyst-free conditions in 75 to 91% overall yields. We study the structural and electronic effect of the carboxylic acid component in the scope of the IMCR reaction.

Keywords: Multicomponent reactions (MCRs); Passerini reaction (P-3CR); α-acyloxycarboxamides

1. Introduction

Multicomponent reactions (MCRs) are a powerful tool for the rapid and efficient construction of novel, complex and structurally diverse compounds from relatively simple structures with minimized production of waste [1,2]. Several tags as a high atom-economy, chemical efficiency, convergence and very high bond-forming-index are attached to MCRs [3]. Isocyanide-based multicomponent reactions (IMCR) have been emerging fields of interest in the last decade, due IMCRs have found numerous applications in the preparation of heterocyclic compounds, combinatorial chemistry, diversity-oriented synthesis, and medicinal chemistry [4].

The Passerini three component reaction (P-3CR) was discovered by Mario Passerini in 1921, it is the first multicomponent reaction based on isocyanide reported, which involving an isocyanide, a carboxylic acid and oxo compound (aldehyde or ketone) in one step to provide α-acyloxycarboxamides which are scaffold that have been found in many natural products and potentially bioactive compounds as depsipeptides which are interesting classes of biopolymers characterized by are analogues of peptides, therefore, making P-3CR as a valuable strategy to obtain α-acyloxycarboxamides [5].

P-3CR is an efficient and environmentally friendly methodology to obtain complex heterocyclic compounds due all benefits that this strategy offered as an atom and time economy, nevertheless there are only few examples involving heterocyclic aldehydes e.g. Ramazani and co-workers in 2014 reported the synthesis of α–(acyloxy)-α–(quinoline-4-yl) acetamides through P-3CR [6]. Although the number of derivatives is wide, it only uses arene carboxylic acids (Scheme 1a). Our methodology (Scheme 1b) has some advantages compared with this work previously reported is the use of an orthogonal bifunctional aldehyde resulting in a functionalized P-3CR adduct that enables a post-transformation process which allows enriched the primary MCR product to finally obtain complex molecules.

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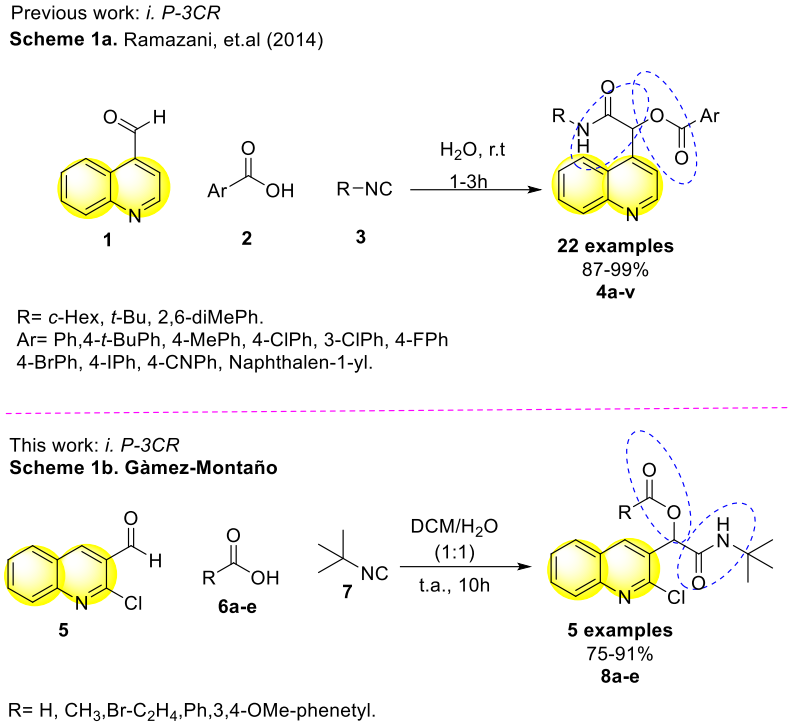


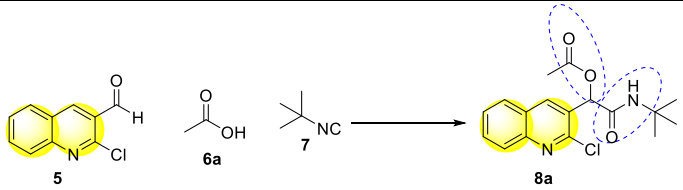
Scheme 1. Previous and present work.

2. Results and Discussion

Following our interests in the efficient synthesis of highly functionalized heterocycles, our work consists of the synthesis of five analogs of α-acyloxycarboxamides that contain the nuclei of 2-chloroquinoline, these analogs were synthesized in excellent yields (75–91%) via the Passerini three-component reaction (P-3CR) under mild green conditions.

We began our investigation by optimizing the Passerini reaction selecting 2-(tert-butylamino)-1-(2-chloroquinolin-3-yl)-2-oxoethyl acetate (**6a**) as our model target to optimize the one-pot process. Firstly, the formation of P-3CR product was attempted by the simple mixing of 2-chloroquinoline-3-carbaldehyde (**5**), acetic acid (**6a**) and terbutyl isocyanide (**7**). The reaction using protic solvents as MeOH, and EtOH (entry 1 and 2, Table 1) and aprotic solvent as DCM (entry 3, Table 1) results in low yields, the use of water as a solvent the reaction we did not obtain the desired product (entry 4, Table 1), while the same reaction with DCM/H_2O (1:1) mixture at room temperature for 10h was more fruitful (entry 5, Table 1). The reactions were monitored by TLC and the isolated product was confirmed by ^{1}H y ^{13}C NMR.

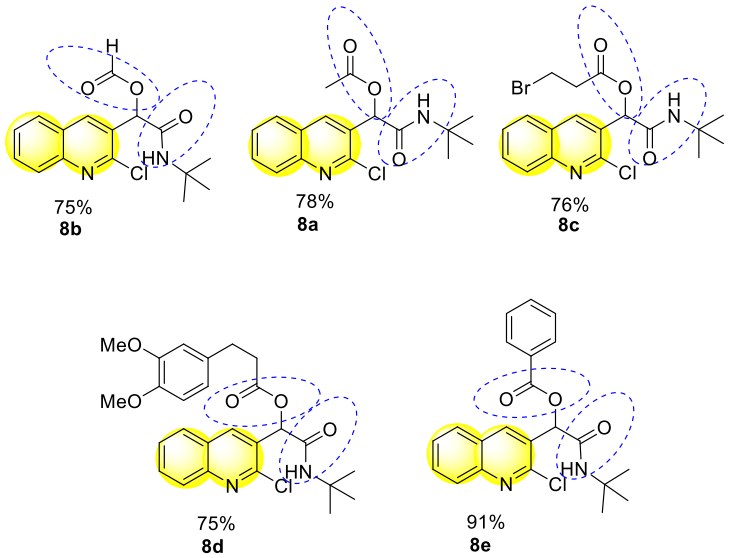
Table 1. Reaction optimizing conditions **8a.**



Entry	Solvent	Energy Source	Time (h)	Yield %
1	MeOH	r.t	29	23
2	EtOH	r.t	27	18
3	DCM	r.t	10	52

4	**H_2O**	**r.t**	**8**	**n.r**
5	**DCM/H_2O (1:1)**	**r.t**	**8**	**78**

Using optimized conditions, the series of five analogs of α-acyloxycarboxamides that contain the nuclei of 2-chloroquinoline were synthesized (shown in Scheme 2). The versatility of the developed methodology was examined using different carboxylic acids as aryl, alkyl and heteroaryl (**6a-e**) and an orthogonal bifunctional aldehyde (2-cloroquinoline—3-carbaldehyde). The respective products 8a–e was obtained in moderate to good yields (63–95%).



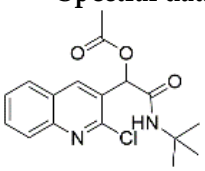
Scheme 2. Substrate scope.

3. Experimental Section

General Information. ^{1}H and ^{13}C NMR spectra were acquired on a 500 MHz spectrometer. The solvent for NMR samples was CDCl3. Chemical shifts are reported in parts per million (δ/ppm). Internal reference for NMR spectra is tetramethylsilane at 0.00 ppm. Coupling constants are reported in Hertz (J/Hz). Multiplicities of the signals are 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.

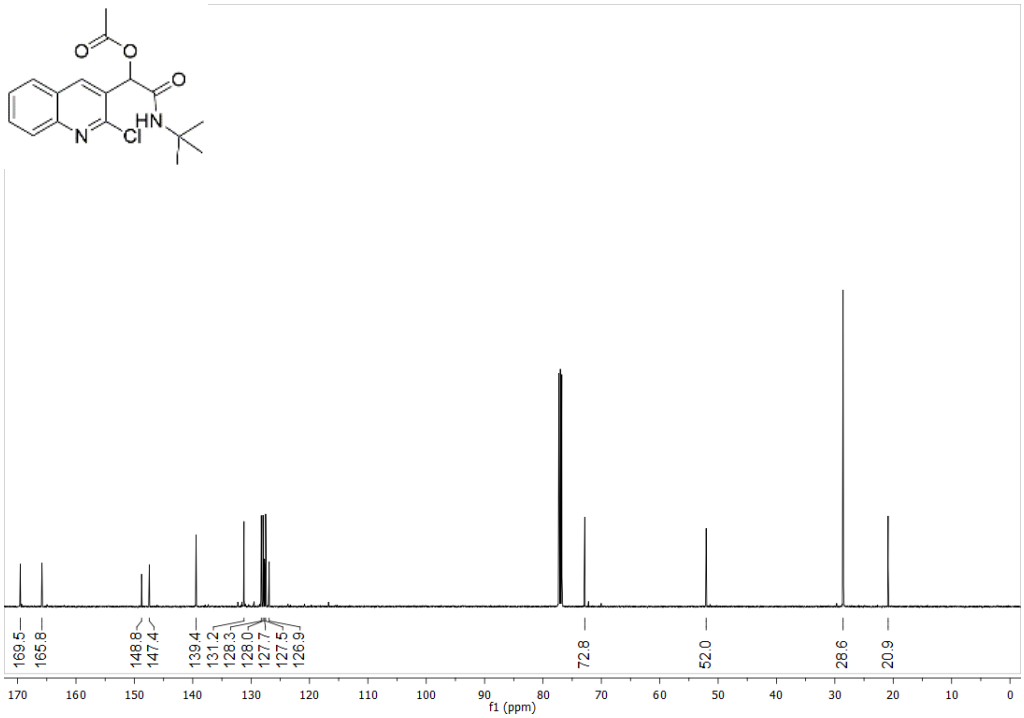
General method: 2-Chloroquinoline-3-carboxaldehyde **5** (0.365 mmol, 1.0 equiv), carboxylic acid **6a-e** (0.365 mmol, 1.0 equiv.) and terbutyl-isocyanide **7** (0.365 mmol, 1.0 equiv.) were dissolved in DCM/H_2O (1:1) mixture were placed in a 10 mL sealed vial. The mixture was stirred at room time for 10 h. Then, the solvent was removed to dryness and the crude was purified by silica-gel column chromatography to afford the products **8a-e**.

Spectral data

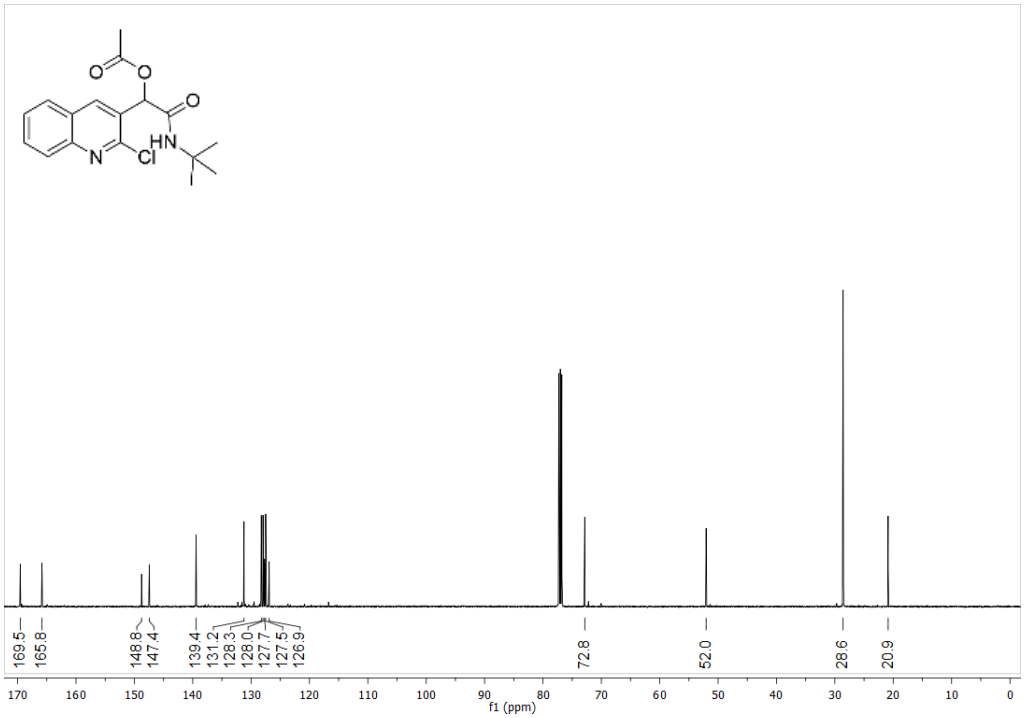


2-(*tert*-butylamino)-1-(2-chloroquinolin-3-yl)-2-oxoethyl acetate (4a): Yield 82% (102.0 mg); white solid; m.p. 147.9-148.1 °C; R_f = 0.33 (Hexanes-AcOEt= 7/3, *v*/*v*); FT-IR

(ATR) $\nu_{máx}/cm^{-1}$ = 3265 cm^{-1}(NH), 1689 cm^{-1}(C=O amide), 1751 cm^{-1} (C=O ester), 1221 cm^{-1}(C-O ester); ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C) δ = 8.30 (s, 1H), 7.91–7.96 (m, 1H), 7.79–7.80 (m, 1H), 7.68–7.69 (m, 1H), 7.48–7.55 (m, 1H), 6.23 (s, 1H), 6.06 (s, 1H), 2.16 (s, 3H), 1.31 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$, 25 °C) δ = 169.5, 165.8, 148.8, 147.4, 139.4, 131.2, 128.3, 128.0, 127.7, 126.9, 72.8, 52.0, 28.6, 20.9; HRMS (ESI^+): *m*/*z* calcd. for $C_{17}H_{19}ClN_2O_3^+$ $[M + H]^+$ 335.1164, found 335.1175.



^{1}H NMR spectrum of compound **8a**



^{13}C NMR spectrum of compound **8a**.

4. Conclusions

The use of orthogonal starting materials in the IMCR allows to synthesize α-acyloxycarboxamides functionalized with a heterocyclic moiety. The variation in nature of carboxylic acid allows increasing the scope of the Passerini reaction. The products could have potential application in post-transformations to access for the generation of more complex molecules.

Author Contributions: All authors contributed equally to this work. All authors have read and agreed to the published version of the manuscript.

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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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