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Graphical Abstract

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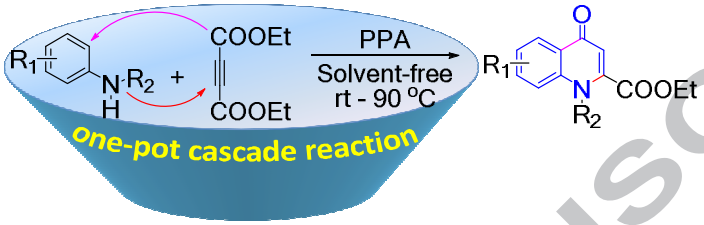

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ABSTRACT

A practical and efficient strategy has been described for the preparation of 4-quinolone derivatives. Using commercially available diethyl acetylenedicarboxylate and aromatic amines as starting materials, the synthetic protocol has been achieved and afforded the product *via* hydroamination at room temperature followed by PPA-catalyzed intramolecular ring closure. The products can be easily obtained in high yields. Conditions and mechanism of the reaction have also been investigated. This protocol is environmentally friendly and transition-metal-free, with advantages including short reaction time, convenient operation and mild reaction conditions.

4-Quinolone is an important nitrogen-containing heterocycle in organic synthesis and medicinal chemistry.[1] Specifically, 4-quinolone is a commonly found core structure in the family of antimicrobial agent such as ofloxacin, norfloxacin,[2] *etc* (Figure 1). Antibacterial drugs containing quinolone moiety gained tremendous importance of clinical application for their properties of broad-spectrum bioactivities, potent pharmacokinetics and unique action mechanism.[3] The development and transformation of these compounds has more than 60 years of history,[4] particularly in recent years, confronting with the arising of drug resistance,[5] antibacterial drugs containing the structure of quinolone has been one of the areas of current research interest.[6] On the other hand, the new discovery of significant biological applications such as, antidiabetic, anticancer and antiviral activities make the development of synthetic methodology to access quinolone compounds continually warranted.[7] Moreover, methods for the efficient assemble of the 4-quinolone skeletons are under-developed.[8]

Currently, cascade reaction is used as a powerful strategy for the generation of small molecules with privileged scaffolds using diversity-oriented synthesis.[9] Usually, several bonds can be formed in a one-pot procedure and complex organic moleculars can be created.[10] One-pot cascade reactions by virtue of their convergence, elegance, and highly step-economy are particularly appealing in the context of rapid target-oriented synthesis. These reactions fall under the fold of green chemistry, as they obviate the isolation and purification of intermediates leading to reduction in pollution.[11] Stimulated by our prior work,[12] we have been interested in method development for the assembly of 4-quinolone compounds with structural diversity by eco-friendly route. Traditional process synthetic routes for quinolones, the Conrad-Limpach and Gould-Jacobs cyclizations were the most frequently employed. They often carried out in several steps, time-consuming, with metal catalysts, or strong acids at high temperature.[13] The harsh reaction conditions made synthesis and isolation of pure products difficult and resulted in low to moderate yields. Thus, the attention and effort of chemists shift to develop new methodologies following green chemistry principles without further complicated and time-consuming purification process and toxic reagents or solvents.[14]

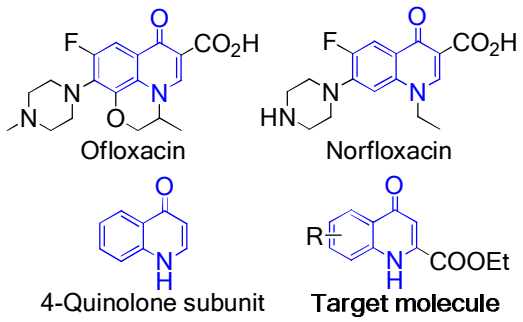

Figure 1. Selected bioactive compounds with 4-quinolone subunits and target molecule.

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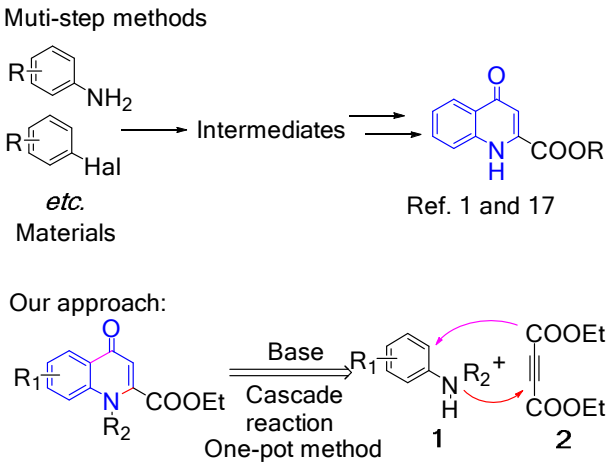


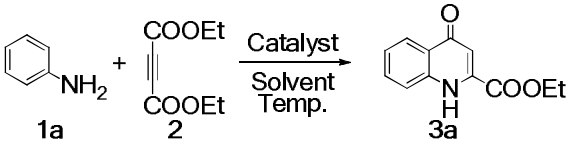
Scheme 1. Strategies for the synthesis of 4-quinolone-2-carboxylates.

We designed a protocol for the construction of 4-quinolone-2-carboxylates *via* a cascade reaction between commercially available aromatic amines **1** and diethyl acetylenedicarboxylate **2** (Scheme 1). We found that amines with dimethyl acetylenedicarboxylate can be used to prepared enamine substrates,[15] which can easy build 4-quinolone-2-carboxylate construction by the Eaton's reagent,[16] but the multi-step, various reagents and catalyst-needed process limited its application.[17] So we report a new green strategy for the construction of 4-quinolone-2-carboxylates *via* an efficient cascade reaction under transition-metal-free conditions, with simple starting materials and mild reaction conditions. The simple post-processing steps illustrated the important academic value and promising application prospect. Moreover, the mechanism through which the solvent-free hydroamination at room temperature and then the intramolecular Friedel-Crafts reaction has been investigated by experiments, which verified one practical and efficient alternative strategy to construct 4-quinolone compounds.

At first, we studied the reaction between the aniline **1a** and the diethyl acetylenedicarboxylate **2**. Under stirring, two materials could quickly react in solvent-free condition at room-temperature. However, the 4-quinolone molecule cannot be judged by ^{1}H NMR analysis. Then we added several catalysts to the reaction mixture after materials completely consumed, tried to get the 4-quinolone in one pot. And we found the concentrated sulfuric acids could enable the reaction mixture to transform 4-quinolone-2-carboxylate.

Next, the aniline **1a** and the diethyl acetylenedicarboxylate **2** were treated to optimize the reaction conditions (Table 1). The reaction could also proceed in different solvents at room temperature (Table 1, entries 2-5), but no better yields we had met. In the elevated temperature treatment, the target product was obtained with higher yields under solvent-free condition (Table 1, entries 6-7). Other catalysts were screened, and we found polyphosphoric acid (PPA) is superior to concentrated sulfuric acids and diphenyl ether (Table 1, entries 7-9). Moreover, the optimal ratio mole of the materials was 1: 1.5 (Table 1, entries 9-12). Thus, we defined the reaction of the phenol **1a** with 1.5 equiv of the diethyl acetylenedicarboxylate **2** catalyzed by PPA under transition-metal-free condition from room-temperature to 90 ^{o}C as the standard reaction conditions (Table 1, entry 9).

Table 1. Optimization of the reaction conditions[a]



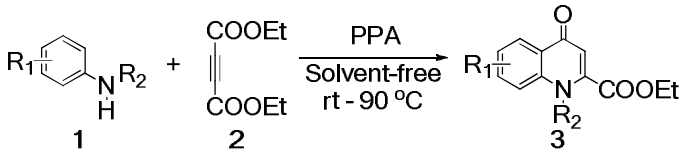
Entry	Catalyst[b]	Solvent	Temp.[c]	**1a**: **2**[d]	Time (h)[e]	Yield (%)[f]
1	H_2SO_4	Solvent-free	rt	1: 1.5	1	15
2	H_2SO_4	Acetone	rt	1: 1.5	2	11
3	H_2SO_4	THF	rt	1: 1.5	2	13
4	H_2SO_4	DCM	rt	1: 1.5	2	11
5	H_2SO_4	Methylbenzene	rt	1: 1.5	2	10
6	H_2SO_4	Solvent-free	90 ^{o}C	1: 1.5	1	22
7	H_2SO_4	Solvent-free	rt-90 ^{o}C	1: 1.5	2	25
8	Diphenyl ether	Solvent-free	rt-230 ^{o}C	1: 1.5	2	6
9	**PPA**	**Solvent-free**	**rt-90 ^{o}C**	**1: 1.5**	**1.5**	**72**
10	PPA	Solvent-free	rt-90 ^{o}C	1:1	1.5	63
11	PPA	Solvent-free	rt-90 ^{o}C	1:2	1.5	73
12	PPA	Solvent-free	rt-90 ^{o}C	2:1	1.5	70

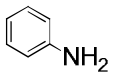
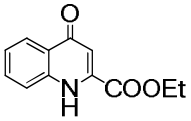
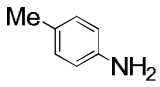
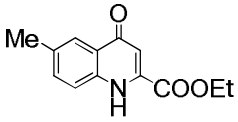
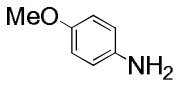
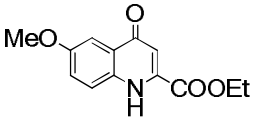
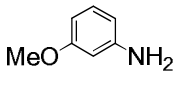
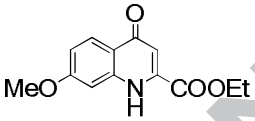
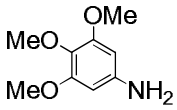
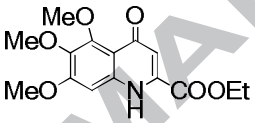
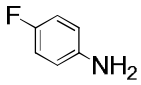
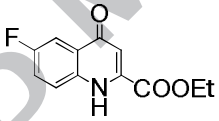
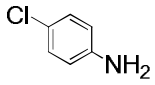
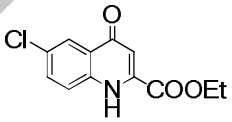
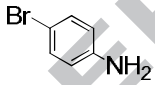
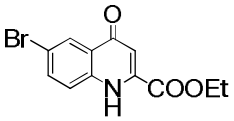
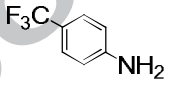
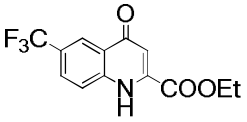
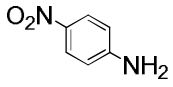
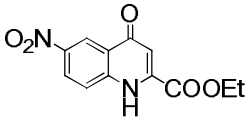
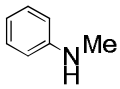
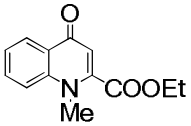
[a] The reaction was carried out using **1a** and **2** in the indicated solvent (1 mL) in a dry Schlenk tube.
[b] The catalysts were added after **1a** completely consumed (10 min).
[c] Temperature was adjusted to different catalysts.
[d] The mole ratio of **1a** and **2**.
[e] The total reaction time.
[f] Isolated yields.

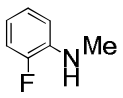
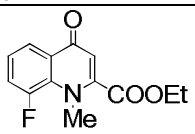
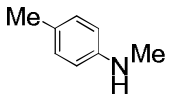
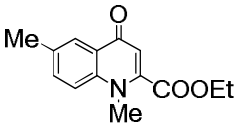
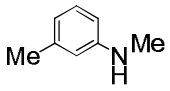
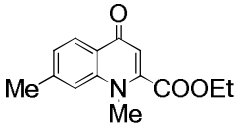
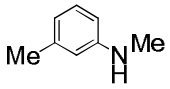
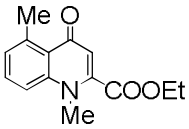
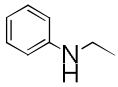
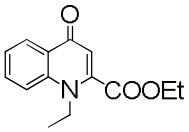
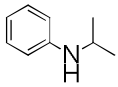
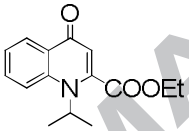
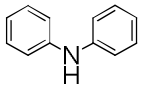
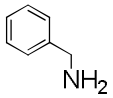
Encouraged by above results, a range of substituted aromatic amines were employed to further study the scope of the protocol with mild conditions. A variety of quinolones derivatives have been obtained from diethyl acetylenedicarboxylate and primary amines or secondary amines by the identical protocol as illustrated in Table 2. They provided good to high yield of 4-quinolone compounds **3**, and all of the products **3a**-**3q** were characterized by IR, ^{1}H NMR, ^{13}C NMR and the high resolution mass spectrometry (HRMS).[18]

An interesting electron density effect of aromatic amines was observed in this reaction, with the yields being increased as the electron density of nitrogen atom increased (Table 2, entries 1, 11, 16 and 17). Notably, primary amines bearing electron-withdrawing group required longer reation time than those containing electron-donating group (entries 2-5 vs 6-10). Similar to primary amines, alkyl group of secondary amines, the presence of which increased the electron density on nitrogen atom, promoted the transformation, whereas the aromatic group exerted an adverse effect (entries 11 and 16 vs 17). And the effect of the steric hindrance and electron density of diphenylamine and benzylamine fail in affording any product (entries 18, 19). The good regioselectivity reaction can also be found in *meta*-substituted primary amines **1d** (entry 4), but poor regioselectivity in *meta*-substituted secondary amine **1n** (entries 14 and 15). These results indicated that the electron density effect of aromatic amines played an important role in the proposed synthetic strategy.

Table 2. Construction of 4-quinolone derivatives

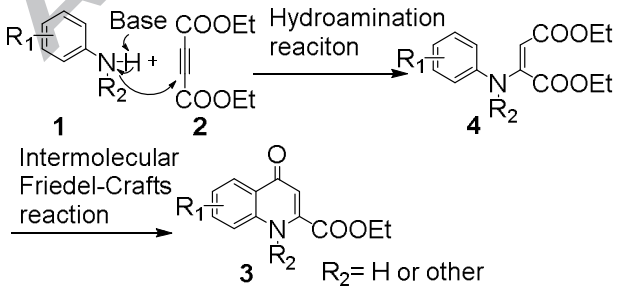


Entry		1		3	Reaction Time (h)	Yield[a] (%)
1	**1a**		**3a**		1.5	72
2	**1b**		**3b**		1	75
3	**1c**		**3c**		1	77
4	**1d**		**3d**		1	84
5	**1e**		**3e**		1	90
6	**1f**		**3f**		1.5	71
7	**1g**		**3g**		1.5	72
8	**1h**		**3h**		1.5	72
9	**1i**		**3i**		1.5	57
10	**1j**		**3j**		1.5	62
11	**1k**		**3k**		1	85

Entry	1		3		Reaction Time (h)	Yield[a] (%)
12	**1l**		**3l**		1.5	70
13	**1m**		**3m**		1	90
14	**1n**		**3n**		1	68[b]
15	**1n**		**3o**		1	30[b]
16	**1o**		**3p**		1	94
17	**1p**		**3q**		1	97
18	**1q**			Complex		
19	**1r**			Complex		

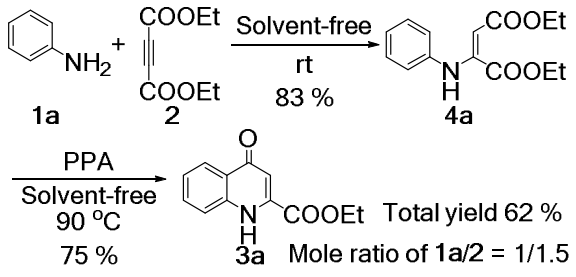
[a] Isolated overall yield for two steps.
[b] Two products in one reaction.

A plausible rationalization for the formation of the desired product **3** is depicted in Scheme 2. As an activated non-terminal alkyne, the lack of electron on the acetylene bond facilitated the hydroamination reaction of diethyl acetylenedicarboxylate with aromatic amine, affording the intermediate **4.** Followingly, the intramolecular Friedel-Crafts reaction of **4** furnished the product **3** with PPA as catalyst.[19] Due to the effect of electron density and steric hindrance of nitrogen atom, the structure of aromatic amine had a significant influence in the protocol.



Scheme 2. Plausible mechanistic pathway for the formation of 4-quinolones **3**.

To understand the mechanism of the cascade reaction process, ethyl 4-oxo-1,4-dihydroquinoline-2-carboxylate **3a** prepared by multi-step method was used instead of one pot protocol to authenticate mechanism (Scheme 3). We found that the intermediate **4a** was easy to obtain from aniline to diethyl acetylenedicarboxylate in a high yield of 83% without any classical solvent at room temperature. Further investigation implied that the target 4-quinolone **3a** was come from **4a**, which was supported by the case that the cascade reaction through nucleophilic addition and Friedel-Crafts reaction. These results also suggest that the cascade reaction is an effective method.



Scheme 3. Two-step synthesis of ethyl 4-oxo-1,4-dihydroquinoline-2-carboxylate **3a**.

In summary, a variety of 4-quinolone derivatives have been quickly synthesized from diethyl acetylenedicarboxylate and aromatic amines by an efficient and practical protocol with mild reaction conditions. This method has been achieved without any classical solvent and simply process afforded the desired product in good to high yield. The result provided reference for the syntheses of drugs containing quinolone moiety, also supplied a basis for the further synthetic methodology research of heterocycles compounds. Our further investigation into the application of the strategy in the formation of quinolone heterocyclic compounds and quinolone drug are currently ongoing.

Acknowledgments

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References and notes

1. (a) Mitscher, L. A. *Chem. Rev.* **2005**, *105*, 559; (b) Asif, M.; Siddiqui, A. A.; Husain, A. *Med. Chem. Res.* **2013**, *22*, 1029.
2. D. T. Chu, P. B. Fernandes, A. K. Claiborne, E. Pihuleac, C. W. Nordeen, R. E. Jr. Maleczka, A. G. Pernet, *J. Med. Chem.* **1985**, 28, 1558.
3. (a) Wiles, J. A.; Bradbury, B. J.; Pucci, M. J. *Expert Opin. Ther. Pat.* **2010**, *20*, 1295; (b) Reddy, G. V.; Kanth, S. R.; Maitraie, D.; Narsaiah, B.; Rao, P. S.; Kishore, K. H.; Murthy, U. S. N.; Ravi, B.; Kumar, B. A.; Parthasarathy, T. *Eur. J. Med. Chem.* **2009**, *44*, 1570.
4. G. Y. Lesher, E. J. Froelich, M. D. Gruett, J. H. Bailey, R. P. Brundage, *J. Med. Pharm. Chem.* **1962**, 91, 1063.
5. Aldred, K. J.; Kerns, R. J.; Osheroff, N. *Biochemistry* **2014**, *53*, 1565.
6. Nilsen, A.; Miley, G. P.; Forquer, I. P.; Mather, M. W.; Katneni, K.; Li, Y. X.; Pou, S.; Pershing, A. M.; Stickles, A. M.; Ryan, E.; Kelly, J. X.; Doggett, J. S.; White, K. L.; Hinrichs, D. J.; Winter, R. W.; Charman, S. A.; Zakharov, L. N.; Bathurst, I.; Burrows, J. N.; Vaidya, A. B.; Riscoe, M. K. *J. Med. Chem.* **2014**, *57*, 3818; (b) Davie, B. J.; Valant, C.; White, J. M.; Sexton, P. M.; Capuano, B.; Christopoulos, A.; Scammells, P. J. *J. Med. Chem.* **2014**, *57*, 5405; (c) Mcguirk, P. R.; Jefson, M. R.; Mann, D. D.; Elliott, N. C.; Chang, P.; Cisek, E. P.; Cornell, C. P.; Gootz, T. D.; Haskell, S. L.; Hindahl, M. S.; Lafleur, L. J.; Rosenfeld, M. J.; Shryock, T. R.; Silvia, A. M.; Weber, F. H. *J. Med. Chem.* **1992**, *35*, 611; (d) Srivastava, N.; Kumar, A. *Eur. J. Med. Chem.* **2013**, *67*, 464.
7. (a) Horchler, C. L.; McCauley, J. P.; Hall, J. E.; Snyder, D. H.; Moore, W. C.; Hudzik, T. J.; Chapdelaine, M. J. *Bioorg. Med. Chem.* **2007**, *15*, 939; (b) Hirano, J.; Hamase, K.; Zaitsu, K. *Tetrahedron* **2006**, *62*, 10065.
8. (a) Lin, J. P.; Long, Y. Q. *Chem. Commun.* **2013**, *49*, 5313; (b) Albrecht, M.; Osetska, O.; Rantanen, T.; Frohlich, R.; Bolma, C. *Synlett.* **2010**, 1081; (c) Genelot, M.; Dufaud, V.; Djakovitch, L. *Tetrahedron* **2011**, *67*, 976; (d) Coltman, S. C. W.; Eyley, S. C.; Raphael, R. A. *Synthesis* **1984**, 2, 150.
9. (a) Barluenga, J.; Rodríguez, F.; Fañanás, F. J. *Chem. Asian J.* **2009**, 4, 1036; (b) M. Ihara, *ARKIVOC* **2006**, 416.
10. (a) Mukherjee, N.; Ahammed, S.; Bhadra, S.; Ranu, B. C. *Green. Chem.* **2013**, *15*, 389; (b) Yao, C.; Qin, B.; Zhang, H.; Lu, J.; Wang, D.; Tu, S. *Rsc Adv.* **2012**, *2*, 3759; (c) Nicolaou, K. C.; Montagnon, T.; Snyder, S. A. *Chem. Commun.* **2003**, 551.
11. (a) Sheldon, R. A. *Chem. Soc. Rev.* **2012**, *41*, 1437; (b) Gawande, M. B.; Bonifacio, V. D.; Luque, R.; Branco, P. S.; Varma, R. S. *Chem. Soc. Rev.* **2013**, *42*, 5522; (c) Anastas, P.; Eghbali, N. *Chem. Soc. Rev.* **2010**, *39*, 301.
12. (a) Huang, C.; Yan, S.-J.; Zeng, X.-H.; Sun, B.; Lan, M.-B.; Lin, J. *RSC Adv.* **2015**, *5*, 17444; (b) Huang, C.; Yin, Y.; Guo, J.; Wang, J.; Fan, B.; Yang, L. *Rsc Adv.* **2014**, *4*, 10188; (c) Huang, C.; Yan, S. J.; He, N. Q.; Tang, Y. J.; Wang, X. H.; Lin, J. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 2399; (d) Huang, C.; Yan, S. J.; Zeng, X. H.; Dai, X. Y.; Zhang, Y.; Qing, C.; Lin, J. *Eur. J. Med. Chem.* **2011**, *46*, 1172; (e) Huang, C.; Yan, S. J.; Li, Y. M.; Huang, R.; Lin, J. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 4665; (f) Yan, S. J.; Huang, C.; Zeng, X. H.; Huang, R.; Lin, J. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 48; (g) Yan, S. J.; Huang, C.; Su, C. X.; Ni, Y. F.; Lin, J. *J. Comb. Chem.* **2010**, *12*, 91.
13. (a) A. A. Boteva, O. P. K. *Chem Heterocycl Comp* **2009**, *45*, 757; (b) Pasquini, S.; Botta, L.; Scincraro, T.; Mugnaini, C.; Ligresti, A.; Palazzo, E.; Maione, S.; Di Marzo, V.; Corelli, F. *J Med Chem* **2008**, *51*, 5075.
14. Cernuchova, P.; Vo-Thanh, G.; Milata, V.; Loupy, A. *Heterocycles* **2004**, *64*, 177.
15. Choudhary, G.; Peddinti, R. K. *Green. Chem.* **2011**, *13*, 3290.
16. Zewge, D.; Chen, C. Y.; Deer, C.; Dormer, P. G.; Hughes, D. L. *J. Org. Chem.* **2007**, *72*, 4276.
17. a) Pandey, A. K.; Sharma, R.; Shivahare, R.; Arora, A.; Rastogi, N.; Gupta, S.; Chauhan, P. M. S. *J. Org. Chem.* **2013**, 78, 1534; b) Borza, I.; Kolok, S.; Galgóczy, K.; Gere, A.; Horváth, C.; Farkas, S.; Greiner, I.; Domány, G. *Bioorgan. Med. Chem. Lett.* **2007**, 17, 406; c) Mazzoni, O.; Esposito, G.; Diurno, M. V.; Brancaccio, D.; Carotenuto, A.; Grieco, P.; Novellino, E.; Filippelli, W. Arch. *Pharm. Chem. Life Sci.* **2010**, 10, 561; d) Coltman, S. C. W.; Eyley, S. C.; Raphael, R. A. *Synthesis*, **1984**, 2, 150; e) Chong, R. J.; Siddiqui, M. A.; Snieckus, V. *Tetrahedron Lett.* **1986**, 27, 5323.
18. General procedure: A mixture of aromatic amines **1** (1.0 mmol) and diethyl acetylenedicarboxylate **2** (1.5 mmol) were stirred at room temperature, and the reaction was observed as indicated by TLC. After completion of the reaction, the reaction mixture was dissolved in 2 mL of PPA followed by temperature rising to 90 °C. The reaction time was shown in Table 2 was performed. After the end of the reaction, the reaction mixture was cooled and disposed in 10 mL of water, and then the crude product was obtained after filtration. The crude mixture was purified by column chromatography on silica gel to afford pure products **3**.
Spectroscopic data for selected compounds:
Ethyl 4-oxo-1,4-dihydroquinoline-2-carboxylate (**3a**): yield 72%; white solid; mp 211–212 °C (Ref. 8d 210–211 °C); IR (KBr) (ν_{max}, cm^{-1}) 3408, 3085, 1735, 1614, 1565, 1518, 1438, 1269, 1074, 861, 746 cm^{-1}; ^{1}H NMR (400 MHz, CD_3Cl): δ 8.34 (1H, s), 7.68-7.64 (1H, m), 7.39-7.39 (1H, m), 7.37-7.35 (1H, m), 7.26 (1H, s), 7.02 (1H, s), 4.48-4.43 (2H, q, J = 8.0 Hz), 1.43-1.39 (3H, m); ^{13}C NMR (100 MHz, CD_3Cl): δ 179.7, 162.9, 139.3, 136.8, 133.1, 126.2, 124.6, 118.4, 111.5, 63.3, 29.7, 14.1; HRMS (ESI-TOF) *m/z* Calcd for $C_{12}H_{11}NO_3$ $[M+Na]^+$ 240.0637, found 240.0631.
Ethyl 1,6-dimethyl-4-oxo-1,4-dihydroquinoline-2-carboxylate (**3m**): Yield 90%; White solid; mp: 100-101 °C; IR (KBr) (ν_{max}, cm^{-1}) 3438, 2978, 1727, 1604, 1482, 1296, 1235, 1074, 852, 810 cm^{-1}; ^{1}H NMR (400 MHz, CD_3Cl): δ 8.14 (1H, br), 7.50-7.48 (1H, m), 7.40-7.39 (1H, m), 6.60 (1H, s), 4.43-4.37 (2H, q, J = 8.0 Hz), 3.78 (3H, s), 2.42 (3H, s), 1.40-1.36 (3H, t, J = 8.0 Hz); ^{13}C NMR (100 MHz, CD_3Cl): δ 178.0, 163.7, 143.7, 139.9, 134.6, 134.2, 126.9, 125.9, 116.0, 112.0, 62.9, 37.2, 20.8, 14.0; HRMS (ESI-TOF) *m/z* Calcd for $C_{14}H_{15}NO_3$ $[M+Na]^+$ 268.0950, found 268.0944..
Ethyl 1-isopropyl-4-oxo-1,4-dihydroquinoline-2-carboxylate (**3q**): Yield 97%; White solid; mp: 98-99 °C; IR (KBr) (ν_{max}, cm^{-1}) 3440, 2977, 1732, 1651, 1470, 1381, 1315, 1241, 1142, 1094, 1027, 854, 764 cm^{-1}; ^{1}H NMR (400 MHz, CD_3Cl): δ 8.42-8.39 (1H, m), 7.74-7.72 (1H, m), 7.66-7.62 (1H, m), 7.37-7.33 (1H, m), 4.68-4.63 (1H, q, J = 8.0 Hz), 4.45-4.39 (2H, q, J = 8.0 Hz), 1.73-1.71 (6H, d, J= 8.0 Hz), 1.42-1.39 (3H, t, J = 7.2 Hz); ^{13}C NMR (100 MHz, CD_3Cl): δ 177.9, 164.5, 145.5, 140.8, 132.1, 127.8, 127.0, 123.8, 118.5, 117.8, 112.2, 62.8, 55.9, 21.6, 14.0; HRMS (ESI-TOF) m/z Calcd for $C_{15}H_{17}NO_3$ $[M+Na]^+$ 282.1106, found 282.1100.
19. a) Kim, H. Y.; Oh, K. *Org. Lett.* **2014**, 16, 5934; b) Wang, T. C.; Chen, Y. L.; Lee, K. H.; Tzeng, C. C. *Synthesis* **1997**, 1, 87; c) Chavan, S. P.; Garai, S.; Dutta, A. K.; Pal, S. *Eur. J. Org. Chem.* **2012**, 6841; d) Richeter, S.; Jeandon, C.; Kyritsakas, N.; Ruppert, R.; Callot, H. J. *J. Org. Chem.* **2003**, 68, 9200.