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Unexpected Simultaneous Synthesis of Trisubstituted Quinolines and Acylhydrazones Under Catalyst-Free Conditions

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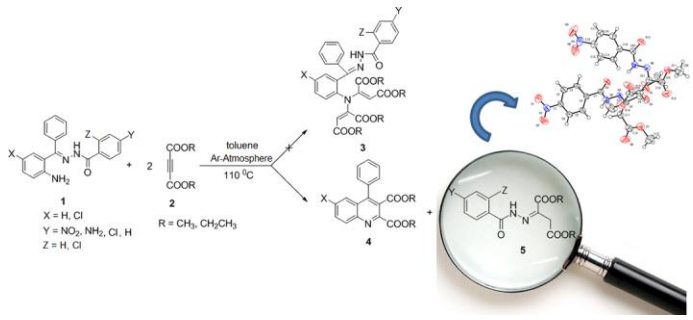
Abstract

Ttrisubstituted quinolines as well as acylhydrazones were unexpectedly prepared from a reaction of N'-((2-aminophenyl)(phenyl)methylene)benzohydrazides with acetylenic esters. Using of N'-((2-aminophenyl)(phenyl)methylene)benzohydrazides led to obtain not only quinoline, but also a second pharmaceutical important product acylhydrazone. Notably, excellent yields, operational simplicity, short reaction times, and the avoidance of the use of catalysts make this approach an attractive complementary method to produce quinoline-2,3-dicarboxylates. The crystal structure of **5a** was determined using single crystal X-ray crystallography. The results showed that crystal packing diagram of **5a** are of two pairs of molecules that have two independent alternate intermolecular 1D-polymeric H-bonds between two perpendicular molecules.

GRAPHICAL ABSTRACT



KEYWORDS: Quinoline-2,3-dicarboxylate; Acylhydrazone; Unexpected simultaneous synthesis; X-ray crystallography; Catalyst free

1. INTRODUCTION

Among nitrogen-containing heterocycles, quinolines have received special attention because of their abundance in a variety of naturally occurring products and medicinally active compounds.[1] A great number of quinoline-based compounds exhibit a broad range of physiological and biological properties such as antimalarial,[2] antitumor,[3] anti-infective,[4] and anti-inflammatory.[5] In agrochemicals,[6] quinoline is a substructure of many herbicides, fungicides, and insecticides. Synthesis of substituted quinolines have been reported using various mechanisms and strategies: Conrad−Limpach−Knorr,[7,8] Skraub−Doebner−Von Miller,[9−11] Frielaender,[12,13a,b] halogen mediated,[14] copper catalyzed[15] and ultrasonic-assisted[16a,b] or miscellaneous.[10,17]

Ring-substituted quinolines have a broad range of applications in medicinal, bioorganic, and industrial chemistry as well as in the field of synthetic organic chemistry.[18] Also, the 4-substituted quinolinecarboxylic acid/ester analogues of these compounds have been found to possess various biological activities like antiparasitic[19] antibacterial[20]

antimycobacterial[21] and antiprotozoal[22] activities. Amongst these analogues 4-substituted quinoline-2,3-dicarboxylates show antiallergic properties[23] and are widely used in the synthesis of bioactive compounds like Benzo[c][2,7]naphthyridines[24] and dihydroxypyridazinoquinolines.[20]

Although there are few reports in the literature for the preparation of 4-substituted quinoline-2,3-dicarboxylates, many of these methods suffer from harsh reaction conditions,[25, 26] long reaction times,[27] low yields,[28] difficulties in workup, and usage of expensive or moisture sensitive catalysts.[29, 30] In view of these drawbacks, the reaction could be further explored and refined to overcome some of these shortcomings under mild reaction conditions.

Acylhydrazones are one of the most important Schiff bases and have been well documented to possess important pharmacological activities,[31a,b] such as antitumor,[32] antibacterial[33] antiviral and antimalarial[31b] effects. Due to the pharmacophoric character of acylhydrazone, this group framework [34] has been widely exploited in the design of new bioactive compounds with different pharmacological profiles.[31a]

In this context, for the first time we present herein an improved methodology that allows simultaneous, simple, and fairly efficient catalyst free synthesis of quinoline-2,3-dicarboxylates and acylhydrazones via the reaction of N'-((2-aminophenyl)(phenyl)methylene)-4-nitrobenzohydrazides with acetylenic esters in toluene at 110 °C.

2. RESULTS AND DISCUSSION

In continuation of our interest aza-Michael reaction,[35a-c] we planned to synthesize compound **3** (R = CH_3, X = H, Y = NO_2, Z = H) from the reaction between N'-((2-aminophenyl)(phenyl)methylene)-4-nitrobenzohydrazide **1** (X = H, Y = NO_2, Z = H, 1 mmol) and dimethyl acetylenedicarboxylate **2** (R = CH_3, 2 mmol). However, when this model reaction was conducted under argon atmosphere in the toluene solvent at 110 °C, two compounds were obtained as reaction products that the spectroscopic data of each of them were inconsistent with expected structure **3**. The structures of the products were deduced from their IR, ^{1}HNMR and ^{13}CNMR. Surprisingly, the data were in good agreement with the structures of unexpected products quinoline-2,3-dicarboxylate **4** (R = CH_3, X = H) and acylhydrazone **5** (R = CH_3, Y = NO_2, Z = H) (Scheme 1).

The reaction was also repeated with one equivalent of **2** under the same conditions. However, after 8 h a mixture of **4**, **5** and unreacted **1** was the only product of reaction and even the prolonged time (24 h) did not lead to completion of this reaction. Based on these results a plausible mechanism can be suggested to this reaction as represented in Scheme 2.

First, Michael addition of **1** to acetylenic ester **2** produces intermediate **6**. This intermediate undergoes a cyclization reaction to **7**. Loss of a hydrazide molecule from **7**, leads to formation of quinoline **4**. The addition of intermediate **8** to ester **2** affords product **5**.

In order to optimize the model reaction conditions, firstly, the effect of ethanol and toluene was investigated as protic and aprotic solvents, respectively, at different reaction temperatures. It was found that the best results were obtained in toluene at 110 °C (Table 1, entry 4).

To survey the scope of the reaction, these optimal conditions were applied for the simultaneous synthesis of trisubstituted quinolines and acylhydrazones derivatives. Different N'-((2-aminophenyl)(phenyl)methylene)-4-benzohydrazides **1** were reacted with acetylenic esters **2** and the results are presented in Table 2. It was found that different substitutions on aromatic ring did not significantly affect the products yield and the reaction time.

3. CONCLUSION

In conclusion, we have described here the first improved methodology that allows simultaneous, simple, and fairly efficient catalyst free synthesis of quinoline-2,3-dicarboxylates and acylhydrazones. This novel catalyst free reaction is attractive in terms of excellent yields, operational simplicity, short reaction times, and mild reaction conditions. For further investigation of compound **5a**, the crystal structure of **5a** is shown in Fig. 1. Crystal packing diagram of **5a** constitute two pairs of molecules that have two independent alternate intermolecular 1D-polymeric H-bonds between two perpendicular molecules Fig. 2.

4. EXPERIMENTAL

4.1. General

All acetylene dicarboxylates, 2-aminobenzophenons and hydrazides were purchased from Merck and used without further purification. The progress of the reactions was followed by TLC using silica gel SILIG/UV 254 plates. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Bruker 400 MHz instrument. FT-IR spectra were recorded on a Perkin-Elmer RX-1 instrument. Elemental analysis for C, H, and N were performed using a Heraeus CHN-O-Rapid analyzer. The melting points were determined in open capillaries with a Stuart Melting Point Apparatus and are uncorrected.

4.2. General Procedure For The Synthesis N'-((2-Aminophenyl)(Phenyl)Methylene)Benzohydrazides (1a-G)

A mixture of 2-aminobenzophenons (1 mmol) and hydrazides (1 mmol) was refluxed in ethanol (10 mL) in the presence of p-toluenesulfonic acid (10 mol%) for 6 h. The progress of reaction was monitored by TLC. At the end of the reaction, the precipitate was collected by filtration and recrystallized from ethanol.

4.2.1. N'-((2-Aminophenyl)(Phenyl)Methylene)-4-Nitrobenzohydrazide (1a)

Orange crystalline solid (0.320 g, 89 % yield); m.p. 234-235 °C; IR (KBr) ν_{max}/cm^{-1}: 3412 and 3340 (NH_2), 3234 (NH), 3058 (C_{sp2}-H), 1676 (C=O), 1637 (C=N); Anal. Calcd. For $C_{20}H_{16}N_4O_3$: C, 66.66; H, 4.48; N, 15.55. Found: C, 66.53; H, 4.55; N, 15.61.

4.3. General Procedure For The Synthesis Of Dialkyl 4-Phenylquinoline-2,3-Dicarboxylates (4a–D) And Dialkyl 2-(2-Benzoylhydrazono)Succinates (5a–G)

A mixture of acetylenic esters **2** (2 mmol) and N'-((2-aminophenyl)(phenyl)methylene)benzohydrazides **1** (1 mmol) was refluxed under argon atmosphere in toluene (5 mL) for 8h. The progress of reaction was monitored by TLC. At the end of the reaction, the solvent was removed under reduced pressure, and produced an oil, which was purified by column chromatography and prep TLC plates (20×20 cm) (Eluent hexane/ethyl acetate 4:1) to give dialkyl 4-phenylquinoline-2,3-dicarboxylates **4** and dialkyl 2-(2-benzoylhydrazono)succinates **5**.

4.3.1. Dimethyl 4-Phenylquinoline-2,3-Dicarboxylate (4a)

White solid (0.289 g, 90 % yield); m.p. 124-126 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.34 (d, *J* = 8.8 Hz, 1H), 7.81–7.86 (m, 1H), 7.60–7.66 (m, 2H), 7.51 (t, *J* = 3.2 Hz, 3H), 7.36–7.38 (m, 2H), 4.10 (s, 3H), 3.65 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.6, 164.5, 147.1, 146.1, 143.8, 133.5, 130.0, 129.8, 129.6, 128.3, 128.2, 127.8, 127.7, 127.3, 126.6, 126.2, 125.6, 52.5, 51.5; IR (KBr) ν_{max}/cm^{-1}: 3069 (C_{sp2}-H), 2994 (C_{sp3}-H), 1746 and 1725 (C=O); Anal. Calcd. For $C_{19}H_{15}NO_4$: C, 71.02; H, 4.71; N, 4.36. Found: C, 71.00; H, 4.70; N, 4.38.

4.3.2. Dimethyl 2-(2-(4-Nitrobenzoyl)Hydrazono)Succinate (5a)

Yellow crystalline solid (0.288 g, 89 % yield); m.p. 146-149 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 13.60 (s, N-H, 1H), 8.35 (d, *J* = 7.6 Hz, 2H), 8.10 (d, *J* = 7.6 Hz, 2H) 3.91 (s, 3H), 3.73 (s, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.8, 127.8, 123.1, 52.1, 51.4, 38.2;

IR (KBr) ν_{max}/cm^{-1}: 3246 (NH), 3052 (C_{sp2}-H), 2959 (C_{sp3}-H), 1734 and 1674 (C=O); Anal. Calcd. For $C_{13}H_{13}N_3O_7$: C, 48.30; H, 4.05; N, 13.00. Found: C, 48.21; H, 3.99; N, 12.94; *m/z* 324 $(M + H)^+$.

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SUPPORTING INFORMATION

Detailed procedures and spectral characterization data for all compounds reported herein can be accessed on the publisher's website.

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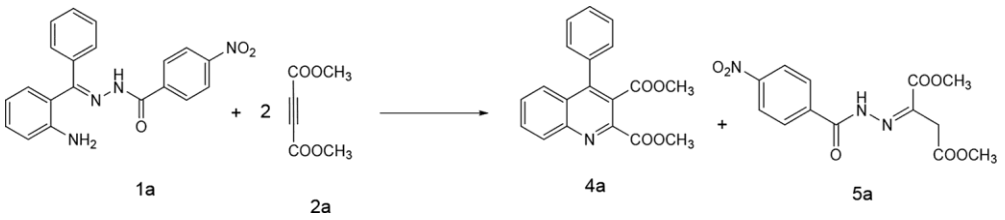
Table 1. Optimization the model reaction conditions[a].



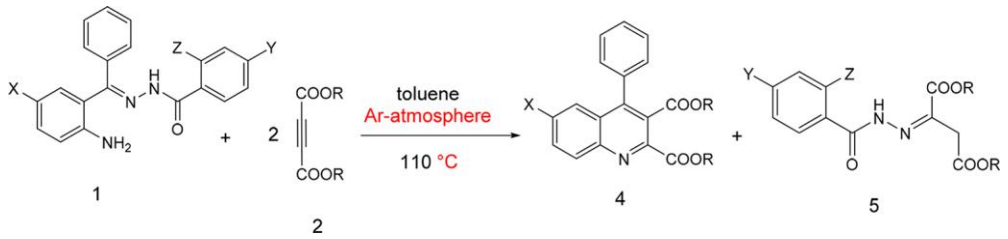
1a 2a 4a 5a

Entry	Solvent	Temp (°C)	Time (h)	Yeild (%)[b]	
				4a	**5a**
1	Ethanol	rt	20	NR	NR
2	Ethanol	100	20	Trace	Trace
3	Toluene	rt	20	<30	<25
4	Toluene	110	8	90	89

[a]Reaction conditions: N'-((2-aminophenyl)(phenyl)methylene)-4-nitrobenzohydrazide (1 mmol), dimethyl acetylenedicarboxylate (2 mmol).

[b]Isolated yield.

Table 2. Synthesis of quinoline-2,3-dicarboxylates **4** and acyl hydrazones **5**[a].

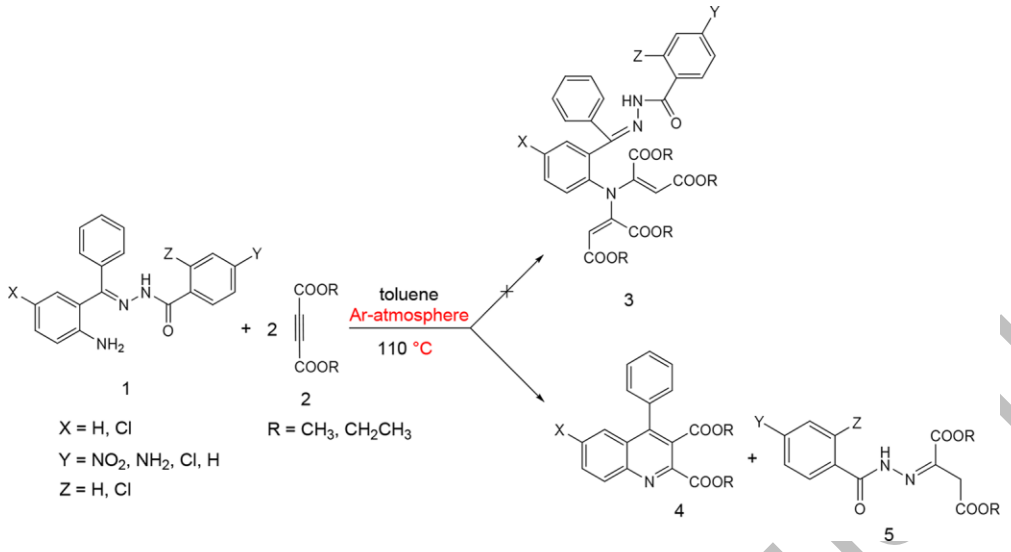


Entry	X	Y	Z	R	Product **4**	Yield (%)[b]	Product **5**	Yield (%)[b]
1	H	NO_2	H	CH_3	4a	90	5a	90
2	H	NO_2	H	CH_2CH_3	4b	89	5b	89
3	Cl	NO_2	H	CH_3	4c	91	5a	90
4	Cl	NO_2	H	CH_2CH_3	4d	90	5b	88
5	H	NH_2	H	CH_3	4a	89	5c	90
6	Cl	NH_2	H	CH_3	4c	90	5c	89
7	H	Cl	H	CH_3	4a	89	5d	90
8	H	H	H	CH_2CH_3	4b	86	5e	90
9	H	Cl	Cl	CH_3	4a	87	5f	89

[a]Reaction conditions: N'-((2-aminophenyl)(phenyl)methylene)benzohydrazides (1 mmol), acetylenic esters (2 mmol), 5 mL of toluene, 8 h, at 110 °C.

[b]Isolated yield.

Scheme 1. The unexpected synthesis of quinoline-2,3-dicarboxylates and acylhydrazones



Scheme 2. Proposed mechanism.

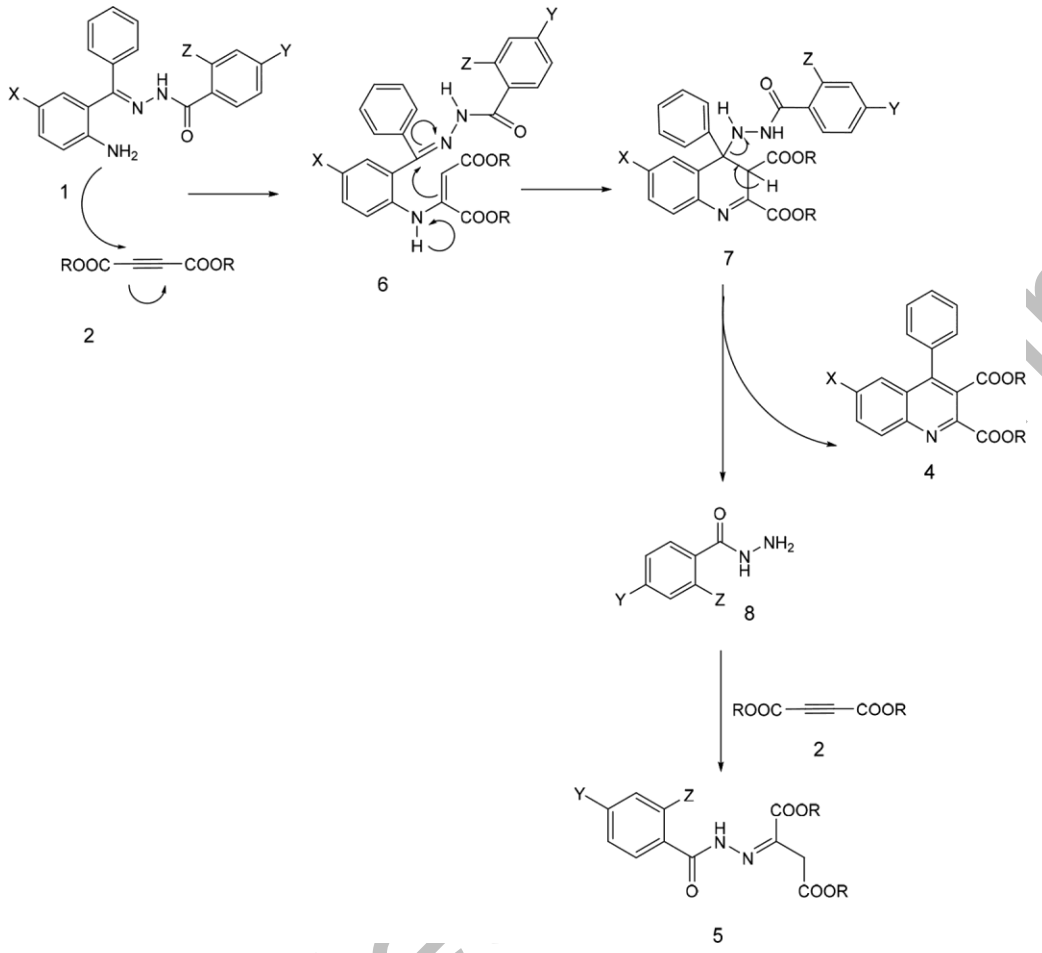


Figure 1. ORTEP diagram of **5a**.

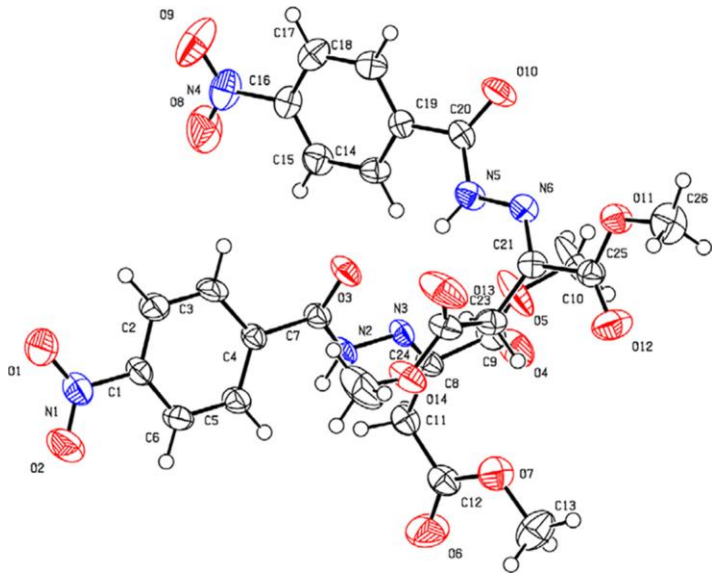


Figure 2. Crystal packing diagram of **5a**.