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Efficient Synthesis of Quinolines via a Knoevenagel/Staudinger/aza-Wittig Sequence

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EFFICIENT SYNTHESIS OF QUINOLINES VIA A KNOEVENAGEL/STAUDINGER/AZA-WITTIG SEQUENCE

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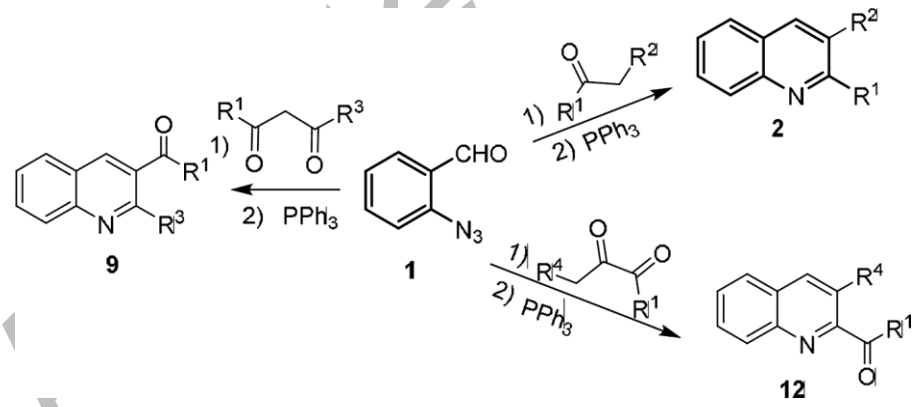
Abstract

A simple and efficient method for the construction of quinoline derivatives from 2-azidobenzaldehyde and various carbonyl compounds was developed. The process involves a Knoevenagel condensation of 2-azidobenzaldehyde with carbonyl compound, and subsequently an intramolecular normal Staudinger/aza-Wittig reaction to form the quinolone ring in satisfactory yields.



KEYWORDS: Quinolones, 2-Azidobenzaldehyde, Knoevenagel/aza-Wittig reaction

INTRODUCTION

Compounds possessing the quinoline skeletons are of great importance due to their versatile biological properties, such as antibacterial,[1,2] antiplatelet,[3] anti-inflammatory[4] and anticancer.[5] Several classical methods have been developed to synthesis quinoline derivatives, such as Skraup-Doebner-von Miller quinoline synthesis,[6] Friedlander synthesis,[7] Pfitzinger-Borsche reaction,[8,9] Conrad-Limpach synthesis[10] and Combes quinoline synthesis.[11] However, these methods usually require harsh reaction conditions or consist of multiple steps, which limited their applications. Transition metal-catalysis also have been employed in order to modify those processes, such as Friedlander quinoline synthesis.[12,13] Very recently Yu and his coworkers report the synthesis of quinolines through an unexpected cascade reaction of Michael/Staudinger/aza-Wittig/aromatization process, which contains the addition and release of nitromethane.[14] Although these methods are effective, most of them suffer from strong acid or base conditions, high reaction temperatures or dull procedures of work-up. So, the development of a simple and efficient methodology for the construction of quinolines is still in need. On the other hand, the method of using aza-Wittig reactions to synthesis of compounds with carbon-nitrogen double bonds has received increased attention in recent years.[15-27] And the tandem Staudinger/aza-Wittig-mediated annulation strategy has also received increased attention due the widely application in the synthesis of heterocyclic compounds.[28,29] Meanwhile, multi-component reactions have undoubtedly become a powerful synthetic tool in the preparation of organic compounds due to their various advantages such as high atom-economy, high time-saving, high structural diversity and molecular complexity over classical multistep methods.[30-36] The combination of multicomponent reactions with aza-Wittig reaction have been utilized in

the synthesis of various heterocyclic molecules.[37-44] Recently we have been interested in the synthesis of various heterocyclic systems especially starting from 2-azidobenzaldehyde.[45,46] Herein, we report a simple and efficient synthesis of quinolines derivatives *via* a Knoevenagel/Staudinger/aza-Wittig sequence starting from 2-azidobenzaldehyde and carbonyl compounds in high yields.

RESULTS AND DISCUSSION

A mixture of 2-azidobenzaldehyde **1** (1 mmol) and carbonyl compound (1 mmol) was stirred in tetrahydrofuran at room temperature in the presence of a catalytic amount of piperidine. The Knoevenagel reaction was carried out smoothly and completed within 2 hours. And then one equiv of triphenylphosphine was added to the mixture at the reflux temperature without the isolation of the Knoevenagel reaction product. At end of the nitrogen evolution of the Staudinger reaction, a reasonable time of heating was given to complete the intramolecular aza-Wittig reaction to afford quinoline derivatives. The results are listed in Table 1 (entries 1-10). The quinoline derivatives were obtained all in moderate to high yields whether the carbonyl compounds that used were alkyl or aryl. The synthesis of quinolines **2** can be viewed as an initial Knoevenagel condensation reaction to form the intermediate **3**, which undergoes the normal Staudinger reaction to give the iminophosphorane **4** as the key intermediate, and finally the quinolines were formed through the intramolecular aza-Wittig reaction under heating conditions (Scheme 1).

In order to expand and evaluate the method for the preparation of quinolines, dicarbonyl compounds were used to take part in the reactions. As exhibited in Table 1, quinolines

were obtained in high yields when 1,3-dicarbonyl compounds were employed (entries 11-14). It is worthy to note that Zhao et al. reported the synthesis of 1H-pyrazolo[1,5-b]indazoles by a domino Staudinger/aza-Wittig cyclization starting from 2-azidobenzaldehyde and active methylene compounds previously, and no quinolines were obtained in their attempts.[47] It's well known that the azide products **5** could react with triphenylphosphine with two different ways under different conditions in the Staudinger reaction. As shown in Scheme 2, 1H-pyrazolo[1,5-b]indazoles **7** were formed via intermediate indazol-2-yl-iminophosphorane **6** when abnormal Staudinger reaction happened.[48,49] On the other hand, the quinoline derivatives **9** were formed through the phenyliminophosphorane **8** when the normal Staudinger reaction happened.[50,51] And when 2,3-dicarbonyl compounds was used as the starting material, quinolines were still the only product and obtained in good yields despite that a selective cyclization may emerged (entries 15-16). It is presumed that quinoline compound **12** appear to be far more stable than **13** because **12** are highly conjugated and their lower activity energy for the formation than **13** (Scheme 3). All the quinoline products are known compounds expect **2i**, **2j** and **2p**, and the spectra of these known compounds are consistent with the literature values.

CONCLUSIONS

In conclusion, we have developed a new and efficient synthesis of quinolines via a Knoevenagel/Staudinger/aza-Wittig sequence. Due to its mild reaction conditions, high yields and simple work-up, the method may serve as an efficient way for construction of

many biologically active quinoline derivatives, and its further application in natural product synthesis is undergoing in our laboratory.

EXPERIMENTAL SECTION

General Procedures

Melting points were determined using a X-4 model apparatus and were uncorrected. MS were measured on a Finnigan Trace MS spectrometer. NMR spectra were recorded on a Bruker Avance III 400 or 600 spectrometer in $CDCl_3$ and chemical shifts (δ) were given in ppm using $(CH_3)_4Si$ as an internal reference ($\delta = 0$). IR were recorded on a PE-983 infrared spectrometer as KBr pellets with absorption in cm^{-1}. Elementary analyses were taken on a Vario EL III elementary analysis instrument. The 2-azidobenzaldehyde and the 1,2,4-triazol carbonyl compound were prepared according to the known methods.[52,53] And all the products (**2a**–**2p**) were confirmed by their spectrum data.

General Preparation Of Quinolines (2a-2p)

To a solution of 2-azidobenzaldehyde **1** (0.44 g, 3 mmol) and catalytic amount of piperidine (2 drops) in dry tetrahydrofuran at room temperature (15 mL), carbonyl compound (3 mmol) in dry tetrahydrofuran (5 mL) was added under nitrogen. The Knoevenagel reaction was carried out smoothly and the condensation was completed within 2 hours. And then triphenylphosphine (0.79 g, 3 mmol) was added to the mixture at the reflux temperature without the isolation of the Knoevenagel product, and with the end of the nitrogen evolution of the Staudinger reaction, the solution was heated at reflux

for a reasonable time to complete the intramolecular aza-Wittig reaction to afford quinoline derivatives. After the completion of the reaction (monitoring by TLC), the solvent was evaporated, and the residue was purified by recrystallization from dichloromethane/ether.

11H-Indeno[1,2-B]Quinoline (2a)

White crystals, mp 168-169 ºC (lit.[54] mp: 166 ºC); ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 8.33-8.20 (m, 3H, Ar-H), 7.84-7.49 (m, 6H, Ar-H), 4.06 (s, 2H, CH_2). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 161.6, 148.0, 145.0, 140.3, 134.5, 131.1, 129.9, 129.0, 128.7, 127.7, 127.4, 127.3, 125.6, 125.4, 122.0, 33.9. MS (m/z, %): 217 (M^+, 100), 203 (80), 127 (67). Anal. Calcd for $C_{16}H_{11}N$: C, 88.45; H, 5.10; N, 6.45; Found: C, 88.38; H, 5.21; N, 6.41.

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SUPPLEMENTAL MATERIAL

Full experimental detail, IR, CHN analysis, mass spectra, and ^{1}H NMR and ^{13}C NMR spectra for this article can be accessed on the publisher's website.

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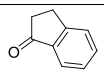
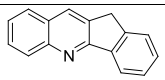
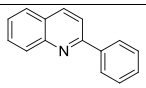
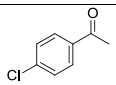
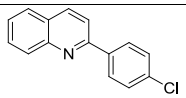
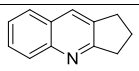
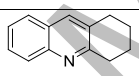
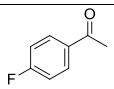
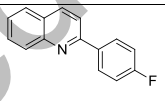
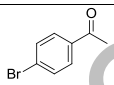
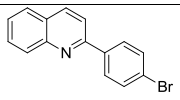
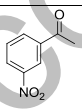
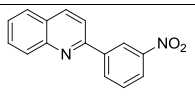
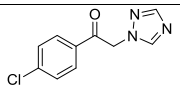
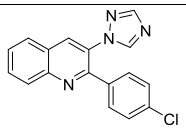
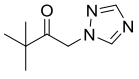
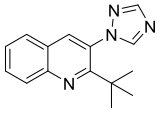
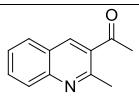
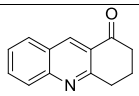
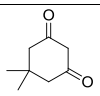
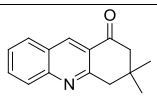
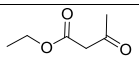
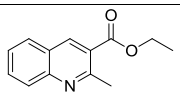
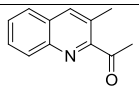
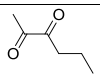
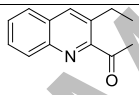
Table 1. Synthesis of quinolines **2** form 2-azidobenzaldehyde **1** and carbonyl compound.

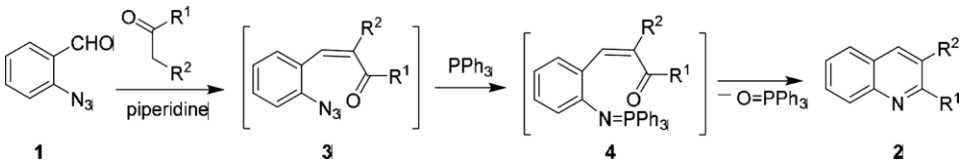
Entry	Carbonyl compound	Product		Heating condition	Yield (%)[a]
1		**2a**		120 min 66 °C	88
2		**2b**		120 min 66 °C	90
3		**2c**		100 min 66 °C	92
4		**2d**		120 min 66 °C	89
5		**2e**		120 min 66 °C	92
6		**2f**		120 min 66 °C	88
7		**2g**		120 min 66 °C	90
8		**2h**		90 min 66 °C	90
9[b]		**2i**		90 min 66 °C	85
10[b]		**2j**		90 min 66 °C	88

11		**2k**		30 min 66 ℃	82
12		**2l**		60 min 66 ℃	88
13		**2m**		60 min 66 ℃	80
14		**2n**		60 min 66 ℃	82
15		**2o**		30 min 66 ℃	80
16		**2p**		30 min 66 ℃	85

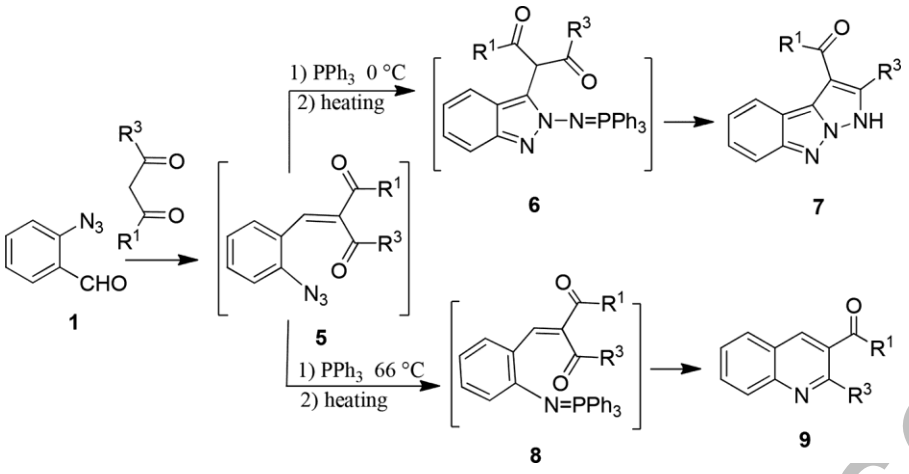
[a]Isolated yields based on 2-azidobenzaldehyde **1**.

[b]1,2,4-triazol carbonyl compound were prepared according to the known methods.

Scheme 1. Synthesis of quinolines form carbonyl compound and 2-azidobenzaldehyde **1.**



Scheme 2. Reactions of 2-azidobenzaldehyde **1** with 1,3-dicarbonyl compounds.



Scheme 3. Reactions of 2-azidobenzaldehyde **1** with 2,3-dicarbonyl compounds.