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An unexpected one-pot synthesis of multi-substituted quinolines via a cascade reaction of Michael/Staudinger/aza-Wittig/aromatization of *ortho*-azido-β-nitro-styrenes with various carbonyl compounds

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ABSTRACT

Multi-substituted quinolines **3** were unexpectedly prepared from a cascade reaction of *ortho*-azido-β-nitro-styrenes with various carbonyl compounds. This method takes advantages of mild condition, simple work-up, high yield as well as wide substrate scope, which makes this method powerful for one-pot synthesis of multi-substituted quinolines.

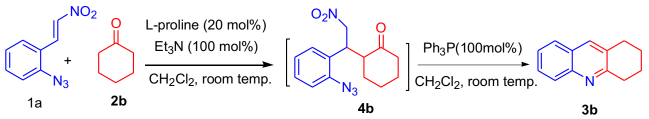
1. Introduction

Quinoline represents an important class of heterocycles since quinoline nucleus has been found in a variety of natural products. Quinoline derivatives possess versatile biological activities, such as anti-malarial, anti-bacterial, anti-asthmatic, anti-hypertensive, anti-inflammatory, anti-platelet, and tyrokinase PDGF-RTK inhibiting activities.[1] Quinoline derivatives can also be used as useful ligands and functional materials,[2] and some of them have been applied in the study of bioorganic and bioorgano-metallic processes.[3] Therefore, quinoline derivatives have become the synthetic targets of many organic and medicinal chemists, and a variety of methods, such as the Skraup, Doebner-Von Miller, Friedländer, and Combes methods have been developed and extended.[4] However, many of these methods reported have some disadvantages, for example, some reactions suffered from high temperatures, prolonged reaction times, harsh conditions, low yields of the products, use of hazardous and/or expensive acidic or basic catalysts and tedious procedures of work-up.

Recently, the aza-Wittig reactions of iminophosphoranes have received much attention for their wide applications in the synthesis of nitrogen-containing heterocycles.[5] These procedures take obvious advantages, such as mild conditions at neutral pH, good yields, and simple work-up. However, there are only a few reports using the aza-Wittig of iminophosphoranes to construct quinoline derivatives,[6] and most of them proceeded in a similar procedure: the intermolecular aza-Wittig reaction of iminophosphorane with isocyanates followed by an intra or intermolecular nucleophilic addition at high temperature. Therefore, development of simple, convenient, and environmentally benign methods for the synthesis of quinolines is in high demand. Herein we report a facile synthesis of multi-substituted quinolines via a cascade Michael/Staudinger/aza-Wittig reaction/aromatization reaction of *ortho*-azido-β-nitro-styrenes with various carbonyl compounds in a one-pot style.

2. Results and discussion

The Michael reaction of ketone to β-nitroolefins have been widely studied, usually L-proline or pyrrolidine-containing catalytic systems were adopted.[7] Firstly, we began our study by using β-nitro-*o*-azidostyrene (**1a**, R=H) and cyclohexanone as model substrates to optimize the reaction conditions (Scheme 1). Initial screening was performed with 20 mol % of L-proline as the catalyst and CH_2Cl_2 as the solvent at room temperature, and the reaction was found very slow and only trace of **3b** was detected after 24 h,



Scheme 1. Preparation of compound **3b**.

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(Table 1, entry 1). Considering that Et_3N may accelerate this type of reaction,[7j] when equimolecular of Et_3N was added as the additive, and indeed, the Michael reaction was accelerated greatly and finished clearly in 2 h (monitored by TLC, entry 2). The adduct was then used for the next step by subsequent addition of stoichiometric triphenyl phosphine without any further purification (for ^1H NMR and ^{13}C NMR data of intermediate **4b**, see the Supplementary data), the iminophosphorane formed via the Staudinger reaction underwent the intramolecular ring-closure via the aza-Wittig reaction at room temperature. Beyond our expectation, the final product was characterized to be the substituted quinoline **3b** in 87% yield (Table 1, entry 2), and the expected product **6b** was not found (Scheme 2). The possible reason is that **6b** can undergo the aromatization to give product **3b** with the release of nitromethane (Scheme 2). However, when 2,2-disubstituted aldehyde (e.g., isobutyraldehyde) was used instead, intermediate **6** could be isolated successfully (^1H NMR and ^{13}C NMR data for **6**, please see Supplementary data).

Table 1
Optimization of the reaction conditions for **3b**[a]

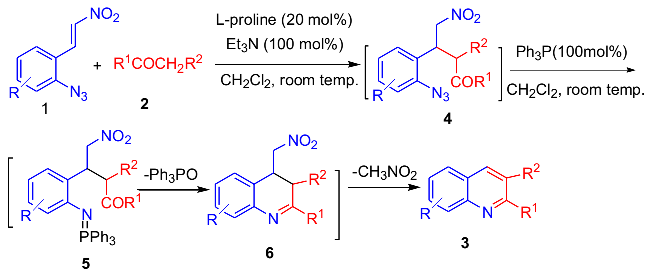
Entry	Catalyst	Additive	Solvent	Yield (%)[b]
1	L-Proline	None[c]	CH_2Cl_2	Trace
2	L-Proline	Et_3N (100 mol %)	CH_2Cl_2	87
3	L-Proline	Et_3N (100 mol %)	EtOH	73
4	L-Proline	Et_3N (100 mol %)	THF	42
5	L-Proline	Et_3N (100mol %)	CH_3CN	78
6	L-Proline	Et_3N (100 mol %)	Toluene	Trace
7	L-Proline	Et_3N (100 mol %)	H_2O	Trace
8	L-Proline[d]	Et_3N (100 mol %)	CH_2Cl_2	75

[a] General conditions: **1a** (0.5 mmol), **2b** (0.6 mmol), L-proline (0.1 mmol), Et_3N (0.5 mmol), solvent (2.0 mL) at room temperature (25 °C) for 2 h; PPh_3 (0.5 mmol), room temperature for another 3 h.

[b] Isolated yields based on **1a**.

[c] The mixture was stirred at room temperature for 24 h.

[d] 10 mol % L-proline was used.



Scheme 2. Preparation of compounds **3**.

The effects of solvents on this cascade reaction in the presence of 20 mol % L-proline as the catalyst and 100 mol % Et_3N as the additive (Table 1, entries 2–7) were then examined. With a solvent of moderate polarity, such as DCM, the reaction gave the best result (Table 1, entry 2). However, protonic solvents, such as ethanol and H_2O, polar non-protonic solvents, such as CH_3CN and THF or low polar toluene were not very effective (Table 1, entries 3–7). When the amount of catalyst was reduced to 10 mol %, the yield of **3b** decreased to 75% (Table 1, entry 8). Thus, the optimized conditions for the synthesis of multi-substituted quinolines were established as following: 20 mol % L-proline was used as the catalyst, the ratio of **1** to carbonyl compound **2** was 1:1.2, 100 mol % Et_3N was used as the additive, CH_2Cl_2 was used as the solvent at room temperature.

With this optimized condition, we explored the substrate scope of the cascade Michael/Staudinger/aza-Wittig reaction/aromatization (Scheme 2, Table 2). It was found that most of reactions proceeded smoothly at room temperature to afford **3** in excellent yields using simple ketones or active methylene compounds (β-carbonyl carboxylate, 1,3-diketone, malonic ester, and ethyl cyanoacetate) as the substrates (Table 2, entries 1–6, 9–12). When butanone was used, the reaction showed good regioselectivity, only 2-ethylquinoline (**3i**) was isolated, and its isomer 2,3-dimethylquinoline was not detected (Table 2, entry 9). It is worth noticing that aliphatic aldehydes, such as phenyl acetaldehyde and propylaldehyde also gave satisfactory results (Table 2, entries 7–8). In contrast, according to the Friendländer procedure, when aliphatic aldehydes were used, the yields of quinolines were very low, which can be due to the self-aldol reaction of these aldehydes.[8] In addition, when *ortho*-azido-β-nitro-styrene (**1b**, R=5-Cl) was used as the substrate, the reactions also gave multi-substituted quinolines **3n** and **3o** in good yields (Table 2, entries 14, 15).

3. Conclusion

In conclusion, we developed a cascade Michael/Staudinger/aza-Wittig reaction/aromatization reaction for the facile synthesis of multi-substituted quinolines. This method has advantages of mild condition, simple work-up, high yield as well as wide substrate scope, which makes this method powerful for the synthesis of muti-substituted quinolines.

4. Experimental

4.1. General

All commercially available solvents and reagents were used without further purification. THF and toluene were distilled from sodium/benzophenone. CH_2Cl_2 and MeCN were distilled from CaH_2. EtOH were distilled from Mg turnings. Et_3N was distilled from KOH. *ortho*-Azido-β-nitro-styrenes **1** was synthesized according to the known procedures.[9] All reactions were performed in oven-dried apparatus under N_2 or argon atmosphere. Analytical thin layer chromatography (TLC) was carried out on silica gel 60 F_{254} plates, visualized by exposure to UV light. Column chromatography purifications were performed under ‘flash’ conditions using 400–630 mesh silica gel. Melting points were determined with a WRS-1B digital melting point apparatus and are uncorrected. ^1H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Varian Mercury PLUS 400 (400 MHz) spectrometer, ^1H NMR chemical shifts were given in δ units relative to TMS (tetramethylsilane) and ^{13}C NMR chemical shifts were reported in parts per million from $CDCl_3$ (taken as 77.0 ppm).

4.2. One-pot synthesis of multi-substituted quinolines 3

All the products are known compounds.

*4.2.1. Ethyl 2-methylquinline-3-carboxylate (**3a**).*[10a,10b] To an oven-dried, 25 mL round-bottom flask equipped with a magnetic bar was added *ortho*-azido-β-nitro-styrene **1** (0.5 mmol, 1.0 equiv), ethyl acetoacetate **2a** (0.6 mmol, 1.2 equiv), L-proline (0.1 mmol, 20 mol %) and NEt_3 (0.5 mmol, 1.0 equiv) in anhydrous CH_2Cl_2 (2 mL) at room temperature. The resulting mixture was then allowed to be stirred for 2 h till the reaction completed (monitored by TLC). Ph_3P (131 mg, 0.5 mmol, 1.0 equiv) was added, and the mixture was stirred for another 3–5 h. The solid formed was filtered off, after the filtrate was concentrated under reduced pressure, the residue was purified by column chromatography on silica gel (eluent: hexane/EtOAc=4:1) to afford **3a** as pale yellow crystals (92.5 mg, 86% yield, mp 69–70 °C; [Lit. 72–72.5 °C]); ^1H NMR (400 MHz, $CDCl_3$): δ=8.75 (s, 1H), 8.05 (d, J=12.0 Hz, 1H), 7.88 (d, J=8.0 Hz, 1H), 7.79 (t, J=8.0 Hz, 1H), 7.55 (t, J=8.0 Hz, 1H), 4.45