

Regioselective *O*-alkylation: synthesis of 1-{2-[(2-chloroquinolin-3-yl)methoxy]-6-chloro-4-phenylquinolin-3-yl}ethanones

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Abstract An efficient and regioselective *O*-alkylation of amides with a variety of electrophiles in the presence of silver nanoparticles is reported as part of our recent research on building blocks for synthesis of natural products. The nano-silver catalyst initiates *O*-alkylation of the amides by heteroalkyl halides. Reaction of equimolar 3-acetyl-6-chloro-4-phenylquinolin-2(1*H*)-one and 2-chloro-3-(chloromethyl)quinolines in the presence of silver nanoparticles in DMSO solution under reflux condition leads to the formation of 1-{1-[2-chloroquinolin-3-yl)methoxy]-6-chloro-4-phenylquinolin-3-yl}ethanones.

Keywords Regioselectivity · Heteroalkyl halides · Quinolone · Silver nanoparticles

Introduction

Major attention has been devoted to the development of regioselective reactions [1–4]. Amides are reported to undergo *O*-alkylation in the presence of metal salt in a suitable solvent. In continuation of the regioselective *N*-alkylation reaction [3], we report here regioselective *O*-alkylation of aromatic amides.

Quinoline derivatives are known to have interesting biological properties ranging from microbial activity to cytotoxicity [5]. Recent studies have, moreover, identified quinolones which inhibit mammalian topoisomerase II [6] as potential lead compounds in the development of anticancer drugs. Quinolines have also been used

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as substituents to impart the desired pharmacological and pharmacokinetic properties to quinolone antibiotics [7].

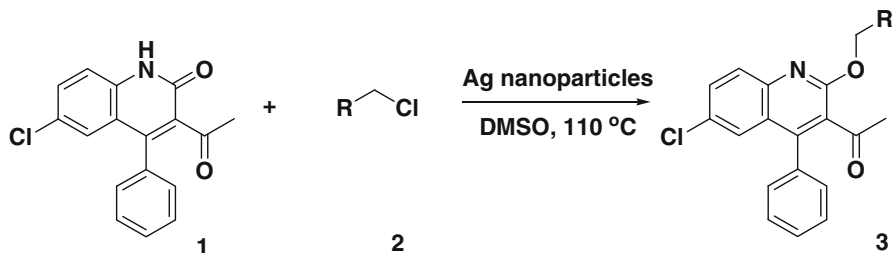
Use of metal salts is of substantial importance in organic synthesis because of high selectivity, enhanced reaction rates, and simple workup. In alkylation reactions, alkali metal salts (K, Na, Li) promote *N*-alkylation whereas silver salts promote *O*-alkylation [8, 9]. In continuation of our work on catalysis and heterocyclics [3, 5, 10–32], we have investigated an *O*-alkylation of 3-acetyl-6-chloro-4-phenylquinolin-2(1*H*)-one with 2-chloro-3-(chloromethyl)quinolines in the presence of silver nanoparticles (Scheme 1).

Results and discussion

The results from synthesis of 1-{1-[2-chloroquinolin-3-yl)methoxy]-6-chloro-4-phenylquinolin-3-yl}ethanones are summarized in Tables 1 and 2. Interestingly, the *O*-alkylation reaction took less time (20–45 min) for completion (Tables 1, 2). The effect of solvent and the scope of the reaction have also been investigated (Table 1). When 1-{1-[2-chloroquinolin-3-yl)methoxy]-6-chloro-4-phenylquinolin-3-yl}ethanones **1** were treated with silver nanoparticles and DMSO with conventional heating in the presence of 2-chloro-3-(chloromethyl)quinoline, **2a**, the product **3a** was obtained in quantitative yield (entry 14, Table 1).

The same reaction carried out with different catalysts in the absence of solvent did not proceed (Table 1, entries 1, 3, 5, 7, 9, 11 and 13). These experimental results clearly suggest that the reaction involves a heterogeneous process and the silver nanoparticles act as an efficient catalyst. The same reaction when carried out with bentonite in DMSO gave two products (Table 1, entry 2), whereas in the presence of silver nanoparticles in DMSO (Table 2, entry 14) only the *O*-alkylated regioselective product **3a** was formed. The results suggest that the reaction proceeds well under the optimized conditions (Table 1, Entry 14). When the *O*-alkylation was carried out in a variety of solvents of different dielectric constant a high yield was obtained in DMSO (high dielectric constant) whereas the *N*-alkylated product was formed in THF (low dielectric constant).

Thus optimization of the reaction suggested that silver nanoparticles with DMSO is the appropriate combination for good regioselective product yield (Table 1). To



Scheme 1 Synthesis of 1-{1-[2-chloroquinolin-3-yl)methoxy]-6-chloro-4-phenylquinolin-3-yl}ethanones (**3a–f**)

Table 1 Optimization of the synthesis of 1-[1-[2-chloroquinolin-3-yl)methoxy]-6-chloro-4-phenylquinolin-3-yl]ethanone **3a**

No.	Catalyst	Solvent	Yield (%) ^a
1	Bentonite	Nil	NR ^b
2	Bentonite	DMSO	25 (trace) ^c
3	Amberlyst	Nil	NR ^b
4	Amberlyst	DMSO	NR ^b
5	Montmorillonite K-10	Nil	NR ^b
6	Montmorillonite K-10	DMSO	Unexpected product
7	Montmorillonite KSF	Nil	NR ^b
8	Montmorillonite KSF	DMSO	NR ^b
9	Kaolin	Nil	NR ^b
10	Kaolin	DMSO	Trace (42) ^c
11	LiCl	Nil	NR ^c
12	LiCl	DMSO	2 (52) ^c
13	Ag ₂ SO ₄	Nil	NR ^c
14	Ag ₂ SO ₄	DMSO	82
15	Ag (0) nanoparticles	DMSO	93

Reactions were carried out with 1.0 equiv **1** and **2a**, 10 mol% catalyst, and 5 mL solvent at 110 °C for 20 min

^a Isolated yield

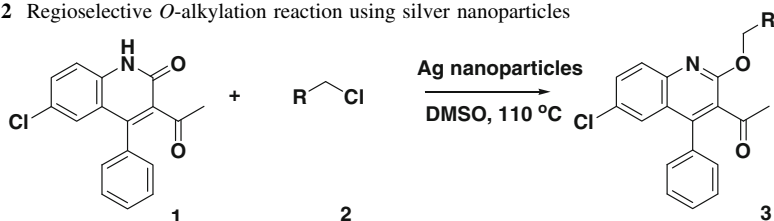
^b No reaction

^c The value in parentheses is for the *N*-alkylated product

investigate the scope of this reaction, a variety of halides were investigated (Table 2, entries 1–7). Substituted 2-chloro-3-(chloromethyl)quinoline **2** afforded the corresponding product **3** in good yields. The proposed mechanism of the reaction is depicted in Fig. 1.

The reaction of silver nanoparticles with alkyl halides may proceed via carbonium ion formation by electrophilic attack by silver on the halogen through an S_N1 mechanism and further reaction of this carbonium ion with amide will take place through covalent bond formation to the most electronegative atom of the ambident anion possessing two different reactive positions. In this reaction, the acetyl group oxygen atom and the amide group oxygen atom share the negative charge whereas the nitrogen atom of the amide group is essentially neutral and hence facilitates the regioselective *O*-alkylation.

In the course of this work, a few compounds with different substitution of the aromatic ring of the quinoline skeleton have been synthesized. Electron-withdrawing groups present in the 3-position of the quinoline ring **1** facilitated the reactions. This method was found to be completely regioselective. The spectral and analytical data of products **3** were in accordance with the assigned structures. Similarly, in all cases the disappearance of the –NH peak confirmed the formation of products **3b–f**.

Table 2 Regioselective *O*-alkylation reaction using silver nanoparticles

Entry	R (2/3)	Product	Time (min)	Yield of 3 (%) ^a
1		3a	20	93
2		3b	30	92
3		3c	25	78
4		3d	30	85
5		3e	45	74
6		3f	40	82

Reactions were carried out on 1.0 equiv **1** and **2** in 5 mL DMSO with 10 mol% catalyst at 110 °C for the specified period of time

^a Isolated yield

Experimental

Solvents and reagents were commercially sourced and used without further purification. Melting points were taken on Elchem microprocessor-based DT apparatus in open capillary tubes and are corrected with reference to benzoic acid. IR spectra were obtained on a Nucon infrared spectrophotometer using KBr pellets. The NMR spectra were recorded on a Bruker Avance 400 MHz spectrometer using TMS as internal standard (chemical shifts δ in ppm). LC-MS was performed with a Flash 1112 analyser in EI mode; the electron energy was 70 eV. Data are reported in the form of m/z intensity relative to the base peak. Silver nanoparticles were

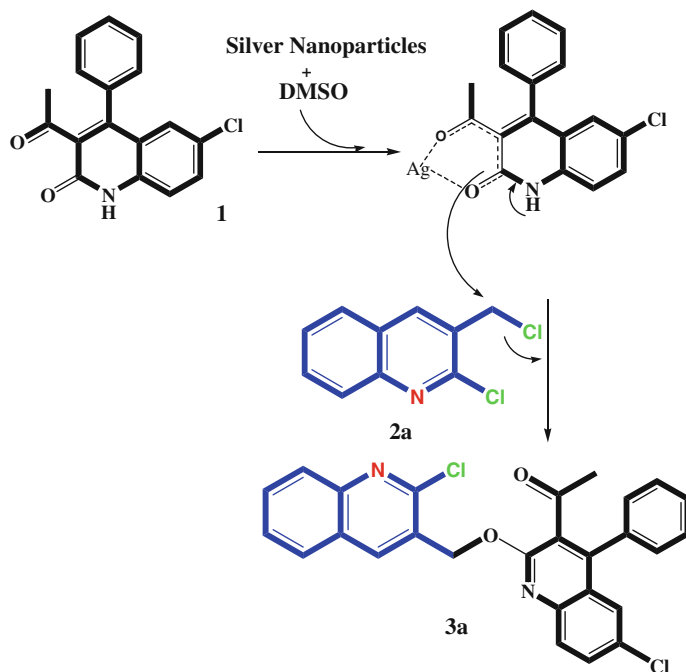


Fig. 1 Proposed mechanism of *O*-alkylation using silver nanoparticles

prepared by use of a reported method [33]. Silver sulfate (1.0 mM, 10 mL) was added dropwise to 30 mL 2.0 mM sodium borohydride solution that had been chilled in an ice bath. The reaction mixture was stirred vigorously on a magnetic stir plate. The solution turned light yellow after addition of 2 mL Ag_2SO_4 , then a brighter yellow, after which the stirring was stopped and the stir bar removed. The clear yellow colloidal solution was then subjected to centrifugation at 5000 rpm for 30 min, after which the pellet were separated and characterized by TEM by use of an Hitachi 800, using an accelerating voltage of 120 kV; a fairly uniform particle size of 25 ± 0.5 nm was evident (Fig. 2).

General procedure for regioselective *O*-alkylation (**3a–f**)

In a typical procedure, heteroalkylhalide **2** (1 mmol) and silver nanoparticles (10 mol%) were added to a solution of the cyclic amide **1** (1 mmol) in DMSO (5 mL) and the mixture was heated under reflux at 110 °C. The reaction was complete within 20–45 min. The reaction mixture was then filtered and the supernatant liquid was added dropwise on to crushed ice. The solution was neutralized with dilute HCl. The precipitate was isolated by filtration and recrystallized from ethanol.

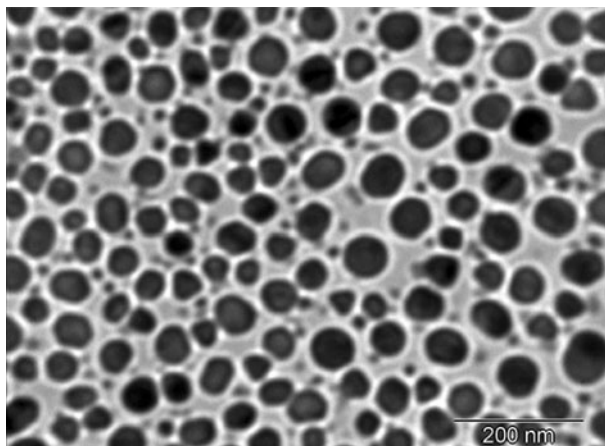


Fig. 2 TEM image of Ag nanoparticles

Synthesis of 1-{1-[2-chloroquinolin-3-yl)methoxy]-6-chloro-4-phenylquinolin-3-yl} ethanones (**3a**)

To a mixture of 3-acetyl-6-chloro-4-phenylquinolin-2(1*H*)-one **1** (1 mmol) and silver nanoparticles (10 mol%) in 5 mL DMSO, 2-chloro-3-chloromethylquinoline **2a** (1 mmol) was added dropwise at 110 °C. Completion of the reaction was monitored by TLC. The reaction mixture was poured into 5% HCl to give 1-{1-[2-chloroquinolin-3-yl)methoxy]-6-chloro-4-phenylquinolin-3-yl}ethanones **3a** as pale yellow solids which were recrystallized from ethanol. Product identity was confirmed by IR, NMR, and MS analysis. Data for new compounds **3a–f**, which have not been reported elsewhere, are given below.

3a: Pale yellow solid, M.p. 167–169 °C, IR (KBr): 1710 cm^{-1} , ^1H NMR (400 MHz, CDCl_3): $\delta_{\text{H}} = 2.22$ (3H, s, $-\text{CH}_3$), 5.84 (2H, s, $-\text{CH}_2$), 7.34 (2H, t), 7.48 (1H, d), 7.52 (3H, t), 7.57–7.67 (2H, m), 7.73 (1H, t), 7.87 (2H, q), 8.03 (1H, d), 8.33 (1H, s) ppm, ^{13}C NMR (125 MHz, CDCl_3): $\delta_{\text{C}} = 32.1$ ($-\text{CH}_3$), 64.7 ($-\text{CH}_2$), 125.5, 126.7, 4 \times 127.0, 2 \times 128.1, 2 \times 129.2, 2 \times 129.3, 2 \times 129.4, 2 \times 130.7, 131.2, 134.1, 136.2, 138.3, 2 \times 144.6, 2 \times 146.3, 201.4 ppm, LC–MS: m/z 473 $[\text{M} + 1]^+$ for $\text{C}_{27}\text{H}_{18}\text{Cl}_2\text{N}_2\text{O}_2$ requires 472.

3b: White solid, M.p. 162–164 °C, IR (KBr): 1708 cm^{-1} , ^1H NMR (400 MHz, CDCl_3): $\delta_{\text{H}} = 2.27$ (3H, s, $-\text{CH}_3$), 2.78 (3H, s, $-\text{CH}_3$), 5.82 (2H, s, $-\text{CH}_2$), 7.23–7.39 (3H, m), 7.44 (1H, d, J 7.6 Hz), 7.47–7.61 (5H, m), 7.69 (1H, d, J 8 Hz), 7.87 (1H, d, J 9.2 Hz), 8.28 (1H, s) ppm, ^{13}C NMR (125 MHz, CDCl_3): $\delta_{\text{C}} = 17.8$ ($-\text{CH}_3$), 32.0 ($-\text{CH}_3$), 64.9 ($-\text{CH}_2$), 125.5, 126.8, 4 \times 127.1, 2 \times 128.2, 2 \times 129.0, 3 \times 129.4, 2 \times 129.6, 2 \times 130.7, 131.0, 134.0, 136.4, 138.3, 2 \times 144.5, 2 \times 146.5, 201.8 ppm, LC–MS: m/z 487 $[\text{M} + 1]^+$ for $\text{C}_{28}\text{H}_{20}\text{Cl}_2\text{N}_2\text{O}_2$ requires 486.

3c: White solid, M.p. 176–178 °C, IR (KBr): 1704 cm^{-1} , ^1H NMR (400 MHz, CDCl_3): $\delta_{\text{H}} = 2.22$ (3H, s, $-\text{CH}_3$), 2.56 (3H, s, $-\text{CH}_3$), 5.81 (2H, s, $-\text{CH}_2$), 7.33 (2H, s), 7.34 (2H, t), 7.40 (1H, d, J 8 Hz), 7.47 (1H, d), 7.52 (2H, m), 7.59 (1H, d,

J 8 Hz), 7.75 (1H, d, *J* 8 Hz), 7.87 (1H, d, *J* 8.8 Hz), 8.26 (1H, s) ppm, LC–MS: *m/z* 487 [M + 1]⁺ for C₂₈H₂₀Cl₂N₂O₂ requires 486.

3d: Pale yellow solid, M.p. 165–167 °C, IR (KBr): 1706 cm⁻¹, ¹H NMR (400 MHz, CDCl₃): δ_H = 2.21 (3H, s, –CH₃), 2.78 (3H, s, –CH₃), 5.84 (2H, s, –CH₂), 7.34 (2H, t), 7.48 (1H, d), 7.52 (2H, t), 7.57–7.67 (2H, m), 7.73 (1H, t), 7.87 (2H, two d), 8.02 (1H, d), 8.31 (1H, s) ppm, LC–MS: *m/z* 487 [M + 1]⁺ for C₂₈H₂₀Cl₂N₂O₂ requires 486.

3e: White solid, M.p. 154–156 °C, IR (KBr): 1706 cm⁻¹, ¹H NMR (400 MHz, CDCl₃): δ_H = 2.24 (3H, s, –CH₃), 3.92 (3H, s, –OCH₃), 5.82 (2H, s, –CH₂), 7.33 (2H, d, *J* 7.6 Hz), 7.41 (2H, d, *J* 8.8 Hz), 7.47–7.51 (2H, m), 7.60 (2H, d, *J* 9.6 Hz), 7.87 (1H, t, *J* 9.6 Hz), 7.90–7.97 (2H, m), 8.73 (1H, s) ppm, ¹³C NMR (125 MHz, CDCl₃): δ_C = 17.8 (–OCH₃), 32.0 (–CH₃), 64.9 (–CH₂), 125.5, 126.8, 4 × 127.1, 2 × 128.2, 2 × 129.0, 3 × 129.4, 2 × 129.6, 2 × 130.7, 131.0, 134.0, 136.4, 138.3, 2 × 144.5, 2 × 146.5, 201.8 ppm, LC–MS: *m/z* 503 [M + 1]⁺ for C₂₈H₂₀Cl₂N₂O₃ requires 502.

3f: Pale yellow solid, M.p. 148–150 °C. IR (KBr): 1708 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ_H = 2.27 (3H, s, –CH₃), 4.05 (3H, s, –OCH₃), 5.82 (2H, s, –CH₂), 6.98 (2H, d, *J* 7.6 Hz), 7.21–7.31 (4H, m), 7.42–7.50 (4H, m), 7.59 (1H, d, *J* 8.4 Hz), 8.73 (1H, s) ppm. LC–MS: *m/z* 503 [M + 1]⁺ for C₂₈H₂₀Cl₂N₂O₃ requires 502.

Conclusion

In the work discussed in this report we developed a simple and effective method for facile *O*-alkylation using silver nanoparticles. The method has very attractive features, for example reduced reaction times, higher yields, and economic viability of the catalyst. The operational simplicity of the procedure is also attractive.

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