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Fe nano particles mediated C–N bond-forming reaction: Regioselective synthesis of 3-[(2-chloroquinolin-3-yl)methyl]pyrimidin-4(3*H*)ones

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ABSTRACT

An efficient and regioselective N-alkylation of 4(3*H*)-pyrimidone with various electrophiles in the presence of Fe nano particle is reported. The catalyst initiates N-alkylation of amides by alkyl chlorides. The reaction of equimolar 4(3*H*)-pyrimidone and 2-chloro-3-(chloromethyl)quinolines in the presence of KOH and Fe nano particle (5 mol %) in DMSO solution under reflux condition formed 3-[(2-chloroquinolin-3-yl]methyl)pyrimidin-4(3*H*)ones.

The C–N bond formation[1,2] is prevalent in the synthesis of numerous compounds that are of biological, pharmaceutical, and material interests. N-Alkylated pyrimidones have been frequently used as intermediates and synthetic precursors for the preparation of a wide variety of heterocyclic compounds (Fig. 1). Many methods for the N-alkylation have been reported.[3–5] Previous methods have been excluded from practical applications due to environmental and economic considerations. Efficient method for N-alkylation is still a challenge. In continuation of our interest in exploring C–C, C–N bond-forming reactions, and catalytic methodology,[6–9] we attempted the nano catalyst-mediated N-alkylation. Catalyst-mediated reactions are well established and have gained popularity as indicated by the large number of papers currently published on this topic.[10,11] The beneficial effects of catalyst-mediated reactions are finding an increased role in the process of chemistry, especially in cases when usual methods require forcing conditions or prolonged reaction times.

While employing traditional addition–elimination chemistry involving hydroxyl analogue of **2** with nucleophile **1**, we were intrigued by the possible application of the Mitsunobu reaction to construct our desired C–N bond and furnish coupled products **3**. The present synthetic route leading to the coupled compounds is summarized in Scheme 1.

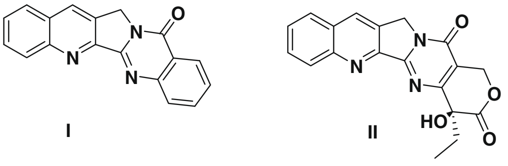
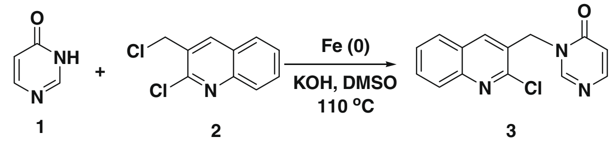


Figure 1. Structures of luotonin A (**I**), azacamptothecin (**II**).



Scheme 1. Synthesis of 3-[(2-chloroquinolin-3-yl)methyl]pyrimidin-4-(3*H*)ones,[13] **3a–g**.

Recently, the use of solid-supported reagents[2] has also received considerable importance in organic synthesis because of their ease of handling, enhanced reaction rates, greater selectivity, simple work-up, and recoverability of catalysts. The efficiency of heterogeneous catalysis in organic synthesis has been improved by employing nano-sized catalysts[12] because of their extremely small size, high surface area, and reactive morphologies. Furthermore, the nano-catalyzed reactions provide the advantages of high atom efficiency, simplified isolation of product, and easy recovery and recyclability of the catalysts.

In accordance with the significance of N-alkylation reaction, various synthetic methods have been developed for the construction of fused heterocycles (Fig. 1). Here we have explored an N-alkylation of 4(3*H*)-pyrimidone with 2-chloro-3-(chloromethyl)-8-methylquinoline in the presence of Fe nano particles to synthesize the synthons of fused heterocycles (Fig. 1).

In view of recent surge in the use of heterogeneous catalysis we have developed N-alkylated pyrimidone employing Fe nano particles as an inexpensive, non-volatile, recyclable, non-explosive, easy to handle, and eco-friendly catalyst (Scheme 1). The results of the synthesis of 3-[(2-chloroquinolin-3-yl)methyl]pyrimidin-4(3*H*)-ones are summarized (Tables 1–3). Interestingly the N-alkylation reaction took less time (30 min) for completion (Tables 1 and 3).

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E-mail address: nawaz_f@yahoo.co.in (Fazlur Rahman Nawaz Khan).

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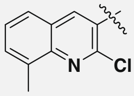
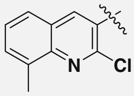
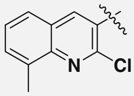
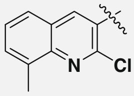
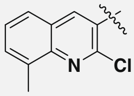
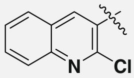
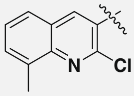
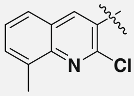
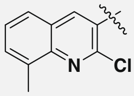
Table 1
Optimization of 3-[(2-chloro-8-methylquinolin-3-yl]methyl)pyrimidin-4-(3*H*)ones[a]

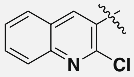
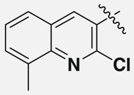
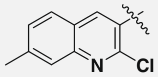
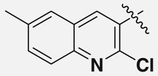
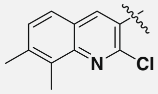
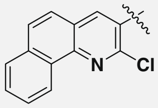
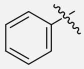
S.no.	R **2b**/**3b**	Condition	Yield (%)[b] **3b**
1		DMF, KO^{t}Bu, THF	35 (trace)[c]
2		KOH, DMSO[d]	NR[e]
3		Fe, DMSO[f]	NR[e]
4		Fe (5 mol %), KOH, DMSO	82
5		Fe (10 mol %), KOH, DMSO	74
6		Fe (15 mol %), KOH, DMSO	63
7		NaH, DMSO	52 (23)[c]
8		NaH, Fe (5 mol %), DMSO	75
9		NaH, Fe (10 mol %), DMSO	63

[a] Reactions were carried out with 1.0 equiv of **1b** and **2b**, 1.5 equiv of base, and nano Fe, 1 mL of solvent, refluxed at 110 °C for the specified time period.
[b] Isolated yields.
[c] The value in parenthesis indicates the O-alkylated product.
[d] The reaction was carried out without nano Fe.
[e] NR = no reaction.
[f] The reaction was carried without base.

Table 2
The effect of solvents on the alkylation of amide

Solvent	KOH (mmol)	RCH$_2$Cl (mmol) **2b**	Yield of **3b** (%)
THF	1	1	40
DMF	1	1	60
DMF/THF	1	1	72
DMSO	1	1	79
DMSO	1.5	1	82

Table 3
C–N bond-forming reaction using Fe(0) nano particles[a]

Entry	R **2**/**3**	Products	Time (min)	Yield[b] (%) **3**
1		**3a**	30	87
2		**3b**	30	82
3		**3c**	40	76
4		**3d**	30	88
5		**3e**	20	84
6		**3f**	30	67
7		**3g**	20	92

[a] Reactions were carried out on 1.0 equiv of **1** and **2**, 1.5 equiv of KOH, 1 mL DMSO, and 5 mol % Fe at 110 °C for the specified period of time.
[b] Isolated yields.

The effect of solvent and reusability of catalyst in synthesis has been explored (Table 2). Scope of the reaction has also been investigated (Table 3). Enhanced reaction rates and improved selectivity were obtained in the presence of nano particles.

The essence of nano catalyst and base can be understood from the following observations, that is, when 4(3*H*)-pyrimidone, **1**, was treated with Fe nano particles and KOH under conventional heating in presence of 2-chloro-3-(chloromethyl)-8-methylquinoline, **2b**, the product **3b** was obtained in quantitative yield (Table 1, entry 4). The same reaction when carried out without either Fe nanoparticles or KOH was not proceeding (Table 1, entries 2 and 3). These experimental results clearly suggest that the reaction involves a heterogeneous process and the catalysis may occur on the surface of the Fe nano particles. These observations were also evidenced from the fact that compounds **1** and **2** were not observed in the organic phase during the reaction, which clearly indicates that the N-alkylation occurs in the pores of nano particles.

In order to ascertain the effect of solvent on N-alkylation, the reaction was carried out using different solvents of varied dielectric constants. The results are summarized (Table 2) which suggest that solvents with high dielectric constant produced high yield of N-alkylated products as in DMSO and that with low dielectric constant formed low yield of N-alkylated product as in the case of THF.

Thus, the DMSO-stabilized Fe nano particles may facilitate the deprotonation/enolate equilibrium of pyrimidone, **1**, thereby reactive enolate is formed which later reacts with heteroaryl alkyl chloride, **2b**, and complete the catalytic cycle by reductive elimination of the product **3b**. The HCl formed is neutralized by the base, KOH. The catalyst regenerated then takes part in further catalysis and improves the product yield. The role of Fe nano particles in the synthesis of 3-[(2-chloroquinolin-3-yl)methyl]pyrimidin-4(3*H*)-one is depicted in Figure 2.

The optimization of the reaction with different amounts of catalyst was carried out and was found that at 5 mol % the yield was good (Table 1). It is evident that the concoction of KOH and Fe nano particles in DMSO solution is the best system in terms of regioselective product yield. The efficiency of the recovered catalyst was verified with the reaction of 2-chloro-3-(chloromethyl)-8-methyl quinoline, **2b**, and 4(3*H*)-pyrimidone, **1**, for the tested three cycles with almost consistent activity (see graph in Supplementary data). These experimental observations suggest the eco-friendly and environmentally benign nature of the reusable iron nano catalyst.

In order to investigate the scope of this reaction, a variety of differently substituted halides were subjected to this reaction (Table 3, entries 1–7). A variety of substituted 2-chloro-3-(chloromethyl)quinolines afforded their corresponding products in good yields. The application of the reaction to simple benzyl halide has also been explored. The results suggest that, irrespective of heteroaryl alkyl halides or benzyl halides, the reaction proceeds well in the optimized conditions (Table 3, entry 4).

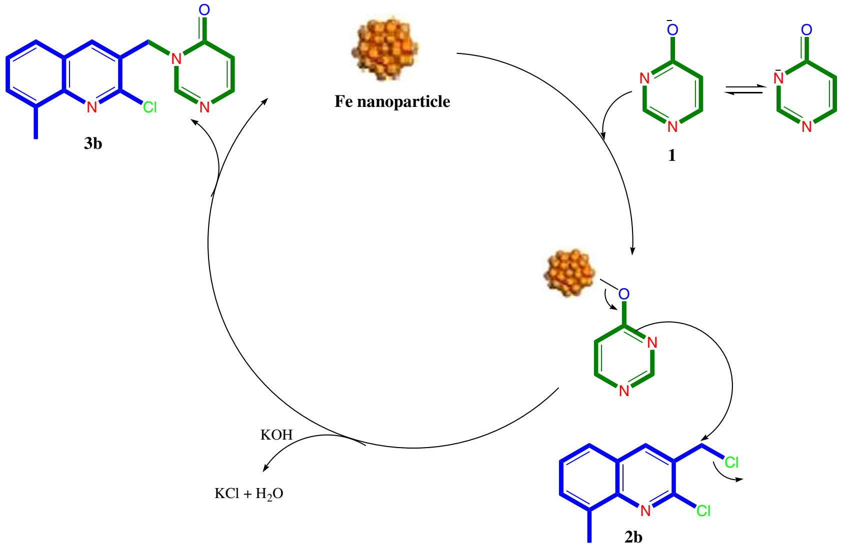


Figure 2. Role of Fe nano particles in synthesis of 3-((2-chloroquinolin-3-yl)methyl)pyrimidin-4(3*H*)-one.

The reaction efficiency by applying strong base such as sodium hydride in DMSO was explored. The result indicates that the alkylation reaction gave a mixture of N-alkylated and O-alkylated products (Table 3, entry 7). The alkylation proceeds through amide/enolate equilibrium. However, the regioselectivity can be achieved by effecting the reaction in the presence of iron nanoparticles (Table 3, entry 8). The amide deprotonation/enolate equilibrium is driven by the presence of iron thereby facilitating the alkylation.

In the course of this work, few compounds with different substitutions in the aromatic ring of the quinoline skeleton have been synthesized. The structures of the substances were corroborated by FTIR, MS, ^{1}H, and ^{13}C NMR spectra. The comparison of the spectra of the N-alkylated compound, **3b**, with those of the O-alkylated product, **3b′**, provided satisfactory evidence for their identification. The ^{1}H NMR spectra displayed considerable confirmation exhibiting chemical shifts for N–CH$_2$ protons (δ 5.34 for compound **3b**) in more up field than that of O–CH$_2$ protons (δ 5.69 for compound **3b′**), similarly chemical shifts for ^{13}C NMR of **3b** shows the appearance of C=O peak at 160 ppm whereas in compound **3b′** C–O appears at 168 ppm due to the inductive effect (see Supplementary data).

TEM image of the Fe nano particles confirmed a fairly uniform particle size of 50 nm (see Supplementary data).

In conclusion, we have developed a simple, convenient, and effective method for the facile N-alkylation using Fe nano particles. The present methodology offers very attractive features such as reduced reaction times, higher yields, and economic viability of the catalyst, when compared with the conventional method. The simple procedure combined with the easy recovery and reuse of this catalyst makes this method an economic chemical process for the N-alkylation. The operational simplicity of the procedure is also attractive. To our knowledge, this is the first report of an efficient general method for N-alkylation by using Fe nano particles. The catalyst can be recovered and reused with no change in the yield.

Acknowledgments

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Supplementary data

Supplementary data (experimental procedure, characterization data ^{1}H and ^{13}C NMR, mass spectra for new compounds, TEM picture of nanoparticle) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.02.128.

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12. Kantam, M. L.; Ramani, T.; Chakrapani Garcoa, L.; Choudary, B. M. *Catal. Commun.* **2009**, *10*, 370–372.
13. In a typical procedure, to a solution of KOH (1.5 mmol) in DMSO (1 mL) solution 4(3*H*)-pyrimidone **1** (96 mg, 1 mmol), 2-chloro-3-(chloromethyl)-quinoline, **3a** (212 mg, 1 mmol), and Fe nano particles (5 mol %) were totted at 110 °C. The reaction was completed within half an hour, and was monitored by TLC. The reaction mixture was then filtered and the supernatant liquid was added dropwise into the crushed ice. The solution was neutralized with dilute HCl and extracted with CHCl$_3$. The excess solvent was removed under vacuum and then subjected to column chromatography to give the desired compound **3a** as a white solid. Spectroscopic data are presented here. Mp 158 °C. $\tilde{\nu}$ = 1681 cm^{-1}. ^{1}H NMR (500 MHz, CDCl$_3$): δ = 4.84 (2H, s), 6.49–6.51 (1H, d, *J* 6.8), 7.56–7.59 (1H, t, *J* 7.2, 7.6), 7.73–7.77 (1H, m), 7.81–7.85 (1H, t, *J* 10.4, 8.0), 7.92–7.95 (1H, t, *J* 5.2, 6.4), 7.99–8.07 (1H, m), 8.24–8.29 (1H, t, *J* 4.4, 13.2), 8.41 (1H, s); ^{13}C NMR (125 MHz, CDCl$_3$) δ = 48.0, 116.3, 126.9, 127.6, 127.7, 128.2, 131.1, 138.7, 140.0, 147.3, 149.1, 151.4, 153.5, 160.8. HRMS: *m*/*z* calcd for $C_{14}H_{10}ClN_3O$, 271.7017; found 271.7801 M$^+$.