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SHORT COMMUNICATION

ZnO nanorods catalyzed *N*-alkylation of piperidin-4-one, 4(3*H*)-pyrimidone, and ethyl 6-chloro-1,2-dihydro-2-oxo-4-phenylquinoline-3-carboxylate

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An efficient ligand-free cross-coupling reaction of 2-chloro-3-(chloromethyl)benzo[*h*]quinoline with *N*-heterocycles such as piperidin-4-one, 4(3*H*)-pyrimidone, and ethyl 6-chloro-1,2-dihydro-2-oxo-4-phenylquinoline-3-carboxylate using a catalytic amount of ZnO nanorods as a recyclable catalyst and KOH as the base in DMSO under reflux at 110 °C is reported.

Keywords: ZnO nanorods, *N*-alkylation, nitrogen heterocycles

Nitrogen heterocycles received considerable attention in literature (Sivasubramanian & Parameswaran, 2007), particularly in terms of the synthetic methodology of their preparation (Chinchilla & Nájera, 2007; Roopan et al., 2008). Among all naturally occurring nitrogen heterocycles, particularly quinoline analogues occupy an important position and have attracted considerable interest because of their significant biological properties such as antimicrobial (Manivel et al., 2008), antioxidant, and cytotoxic properties (Roopan & Khan, 2009). The chemistry and applications of *N*-alkylation have recently received much attention due to their usefulness as building blocks in organic synthesis (Nacro et al., 2007). Many *N*-alkylation methods have been reported (Eltsov et al., 2000). However, many of these procedures are not satisfactory with regard to practical applications due to environmental and economic considerations.

An efficient *N*-alkylation method is still a challenge. Designing new specific catalysts and exploring their catalytic activity has caused profound effects on the optimization of the efficiency of a wide range of organic syntheses (Mirjafary et al., 2008). Recently, nanocrystalline inorganic oxides attracted interest because of their different topical characteristics (Alonso et al., 2008). In the last few years, literature has highlighted the importance of nanosized materials in several scientific and technological areas (Richards et al., 2000). Development of such catalysts has resulted in more economical and environmentally friendly chemistry replacing unstable or toxic catalysts.

Therefore, in continuation of our attempts to develop environmentally benign protocols (Roopan et al., 2008, 2009b; Roopan & Khan, 2009), we report for the first time ZnO nanorods catalyzed *N*-alkylation of piperidin-4-one, 4(3*H*)-pyrimidone, and ethyl 6-chloro-1,2-dihydro-2-oxo-4-phenylquinoline-3-carboxylate (Fig. 1). The nanorods of ZnO were prepared applying a reported procedure (Kawano & Imai, 2008) and confirmed by HRSEM (Fig. 2).

Glassware was dried in hot air-oven prior to use. All other reagents were purchased from Aldrich Co. (India), Melting points were taken in open capillary tubes and were corrected with reference to benzoic acid.

For the preparation of aldehyde *I* and hydroxymethyl derivative *II*, reported procedures were used (Khan et al., 2009a, 2009b; Roopan et al., 2009a). Compound *II*, on reaction with thionyl chloride, gave the corresponding chloromethyl derivative *III*.

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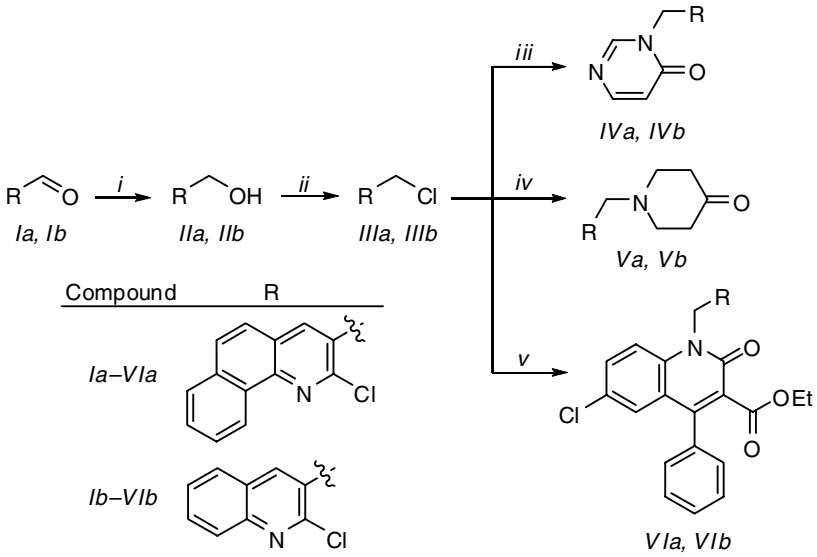

Fig. 1. Synthesis of *N*-alkylated heterocycles. Reagents and conditions: *i*) $NaBH_4$, MK-10, MW 500 W, 4–5 min; *ii*) $SOCl_2$, reflux, 30 min; *iii*) 4(3*H*)-pyrimidone, 5 mole % of ZnO nanorods, KOH, DMSO, 110 °C; *iv*) piperidin-4-one, 5 mole % of ZnO nanorods, KOH, DMSO, 110 °C; *v*), ethyl 6-chloro-1,2-dihydro-2-oxo-4-phenylquinoline-3-carboxylate, 5 mole % of ZnO nanorods, KOH, DMSO, 110 °C.

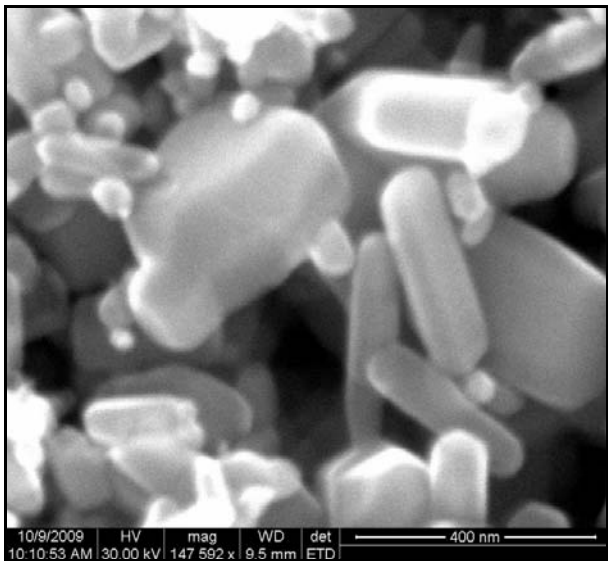

Fig. 2. SEM image of ZnO nanorods.

IR measurements were done using KBr pellets for solids on a Nucon Infrared spectrophotometer. NMR spectra were recorded on a Bruker Spectrospin Advance III 500 MHz (AV 500) spectrometer with TMS as internal standard. Column chromatography was carried out using silica gel (60–120 mesh). High resolution scanning electron microscope (HRSEM) spectra were recorded on a FEI Quanta FEG 200. Mass spectra were recorded on a Finnigan MAT 8230 spectrometer.

General procedure for the synthesis of *N*-alkylated products *IV*–*VI* was applied. Zinc oxide nanorods (5 mole %) were added to a stirred solution of *N*-heterocycle (1 mmol of piperidin-4-one, 4(3*H*)-pyrimidone, ethyl 6-chloro-1,2-dihydro-2-oxo-4-phenylquinoline-3-carboxylate, respectively) in DMSO (2 mL), then KOH (1.5 mmol) was added portionwise followed by an addition of arylalkyl chloride *III* (1 mmol) and the reaction mixture was refluxed at 110 °C for 30 min. The reaction mixture was then cooled and poured on crushed ice. The precipitate was filtered, washed with H_2O and dried in air. The crude product was chromatographed on a column of silica gel using a petroleum ether/ethyl acetate (φ_r = 85 : 15) mixture as an eluent which afforded product *IV* in a good yield. Compounds *V* and *VI* were obtained and purified by a similar procedure (Tables 1 and 2).

Structures of all derivatives were confirmed by ^1H and ^{13}C NMR, HRMS, and IR spectral analyses. Spectral data of the new compounds are given in Table 3.

In a preliminary reaction, 2-chloro-3-(chloromethyl)benzo[*h*]quinoline (*IIIa*) treated with 4(3*H*)-pyrimidone in the presence of 5 mole % of ZnO nanorods (Fig. 1) and KOH (1.5 eq) in DMSO (2.0 mL) gave the corresponding *N*-alkylated product *IVa*.

To optimize the reaction conditions, different bases were used for the reaction of *IIIa* with 4(3*H*)-pyrimidone (Table 1). The mixture of ZnO nanorods, KOH, and DMSO provided *N*-alkylated products *IV*–*VI* in moderate to excellent yields (Table 1, entry 6) whereas in the presence of other bases lower yield were obtained (Table 1, entries 1, 2). This reaction when carried out in the absence of ZnO nanorods or a base was not futile (Table 1, entries 1, 7, 8).

Moreover, an optimized amount of 5 mole % of ZnO nanorods was required for the reaction (Table 1, entries 2–6). To check recyclability, the catalyst was centrifuged from the reaction mixture, washed with

Table 1. Optimization of 3-((2-chlorobenzo[*h*]quinolin-3-yl)methyl)pyrimidin-4(3*H*)-one (*IVa*) synthesis[a]

Entry	Optimized parameters		Yield/%[b]
	Catalyst, base, solvent	Time/h	
1	ZnO nanorods, DMSO[c]	1	nr
2	ZnO nanorods (5 mole %), NaOH, DMSO	0.5	65
3	ZnO nanorods (5 mole %), *tert*-BuOK, DMSO	0.5	72
4	ZnO nanorods (5 mole %), KOH, DMSO	0.5	87
5	ZnO nanorods (10 mole %), KOH, DMSO	0.5	76
6	ZnO nanorods (15 mole %), KOH, DMSO	0.5	74
7	DMF, *tert*-BuOK, THF	1	30
8	KOH, DMSO[d]	1	nr

a) Reaction conditions: 1.0 eq of *IIIa*, 4(3*H*)-pyrimidone, 1.5 eq of base, 1.5 eq of ZnO nanorods, 110 °C, specified reaction time; *b*) isolated yields; *c*) reaction run without base; *d*) reaction run without nanorods; nr = no reaction.

Table 2. Characterization data of newly prepared compounds

Compound	Formula	M_r	Yield/%	M.p./°C	Appearance
IVa[a]	$C_{18}H_{12}ClN_3O$	321.7603	87	195	White powder
IVb[a]	$C_{14}H_{10}ClN_3O$	271.7017	84	158	White powder
Va	$C_{19}H_{17}ClN_2O$	324.8040	72	–	Pale yellow gummy
Vb	$C_{15}H_{15}ClN_2O$	274.7454	82	78	Pale yellow powder
VIa	$C_{32}H_{22}Cl_2N_2O_3$	553.4347	82	235	White powder
VIb	$C_{28}H_{20}Cl_2N_2O_3$	503.3760	62	202	White powder

a) Spectral data matched with the authentic samples (Roopan et al., 2010).

Table 3. Spectral data of newly prepared compounds

Compound	Spectral data
Va	IR, $\tilde{\nu}$/cm^{-1}: 1718 (C═O) ^{1}H NMR (DMSO-d_6), δ: 2.55 (t, 4H), 2.94 (t, 4H), 3.93 (s, 2H), 7.70–7.77 (m, 3H), 7.86 (d, 1H, J = 9.0 Hz), 9.22 (t, 1H), 7.93 (t, 1H), 8.31 (s, 1H) ^{13}C NMR (DMSO-d_6), δ: 41.1 (2C), 53.0 (2C), 58.0, 124.3, 124.5, 125.3, 127.2 (2C), 127.6 (2C), 128.5, 130.2, 133.5, 137.8, 145.3, 149.7, 208.13 HRMS, m/z (found/calc.): 324.8181/324.8040 (M^+, $C_{19}H_{17}ClN_2O$)
Vb	IR, $\tilde{\nu}$/cm^{-1}: 1712 (C═O) ^{1}H NMR (DMSO-d_6), δ: 2.50–2.53 (t, 4H), 2.91–2.92 (t, 4H), 3.86 (s, 2H), 7.55–7.59 (m, 1H), 7.70–7.74 (m, 1H), 7.84 (d, 1H, J = 8.4 Hz), 8.02 (d, 1H, J = 8.4 Hz), 8.27 (s, 1H) ^{13}C NMR (DMSO-d_6), δ: 41.2, 45.5, 53.1, 58.2, 127.0, 127.1, 127.3, 127.3, 128.2, 130.1, 130.2, 137.9, 146.9, 150.9, 208.5 HRMS, m/z (found/calc.): 274.0193/274.7454 (M^+, $C_{15}H_{15}ClN_2O$)
VIa	IR, $\tilde{\nu}$/cm^{-1}: 1712 (C═O) ^{1}H NMR (DMSO-d_6), δ: 1.03–1.05 (t, 3H, CH_3), 4.17–4.18 (d, 2H, CH_2), 5.94 (s, 2H, CH_2), 7.41–7.43 (t, 2H), 7.51–7.55 (m, 4H), 7.62–7.64 (m, 1H), 7.70–7.78 (m, 3H), 7.84–7.93 (m, 3H), 8.41 (s, 1H), 9.24–9.26 (d, 1H) ^{13}C NMR (DMSO-d_6), δ: 13.7, 61.5, 64.4, 124.56, 124.58, 124.9, 125.3, 125.4 (2C), 127.2 (2C), 127.6 (2C), 128.2 (2C), 128.5 (2C), 128.8, 129.10, 129.14, 129.4, 130.2, 130.6, 131.2, 133.6, 134.3, 136.7, 144.7, 148.0, 148.3, 156.8, 165.7 HRMS, m/z (found/calc.): 553.4346/553.4347 (M^+, $C_{32}H_{22}Cl_2N_2O_3$)
VIb	IR, $\tilde{\nu}$/cm^{-1}: 1732 (C═O) ^{1}H NMR (DMSO-d_6), δ: 1.01 (t, 3H, CH_3), 4.13 (m, 2H), 5.86 (s, 2H, CH_2), 7.25–7.38 (m, 2H), 7.49–7.62 (m, 6H), 7.70–7.74 (t, 1H), 7.82–7.87 (m, 2H), 8.03(d, 1H, J = 8.4 Hz), 8.36 (s, 1H) ^{13}C NMR (DMSO-d_6), δ: 13.7, 61.6, 64.4, 119.6, 125.0, 125.5 (2C), 127.1 (2C), 127.6, 128.3 (2C), 128.5 (2C), 129.0 (2C), 129.2, 130.3, 130.7, 131.3, 134.4, 137.0, 144.8, 147.1, 148.4, 149.2, 156.8, 165.7 HRMS, m/z (found/calc.): 503.8797/503.3760 (M^+, $C_{28}H_{20}Cl_2N_2O_3$)

water, and dried in vacuum. It could then be reused for further catalytic reactions without any change in its catalytic activity.

These experimental results clearly suggest that nanoparticles adsorbed on the nitrogen atom of the heterocycle in ring nitrogen of the amines (see reaction

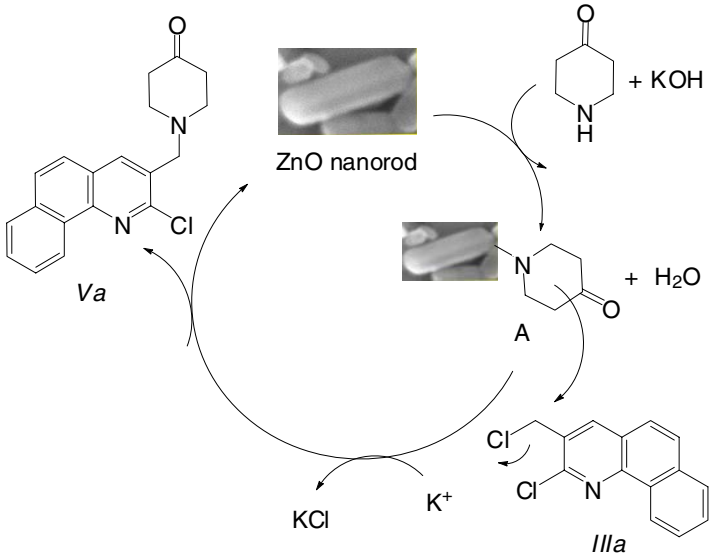

Fig. 3. Role of ZnO nanorods in the synthesis of *N*-alkylated products.

conditions *iv* in Fig. 1) produce intermediate A (see Fig. 3) which can be further involved in the coupling of arylalkyl chloride *IIIa* to give product *Va* (Fig. 3).

In this communication, a simple method of the *N*-alkylation of some heterocycles using ZnO nanorods is reported. A simple experimental procedure combined with an easy workup and excellent yields of products are salient features of the presented method.

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